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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

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MANAGEMENT OF SURGICAL CONDITIONS OF THE ALIMENTARY TRACT IN INFANCY

Transcription of a Panel Meeting on Therapeutics

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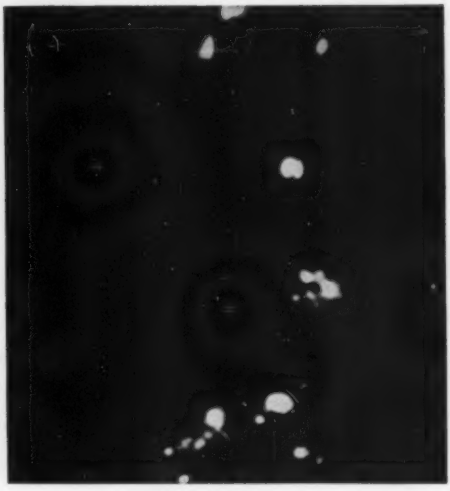

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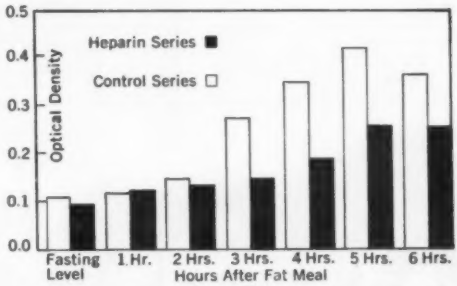
2. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959.



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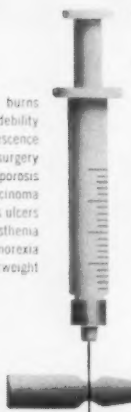

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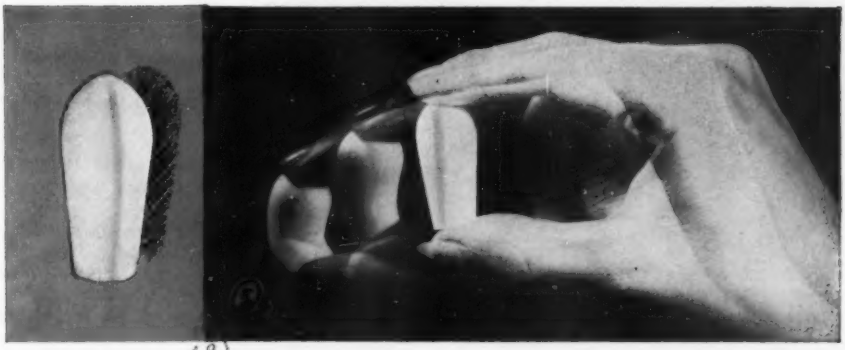

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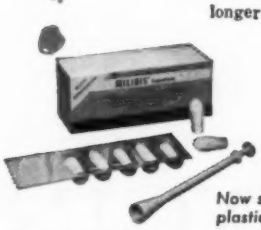

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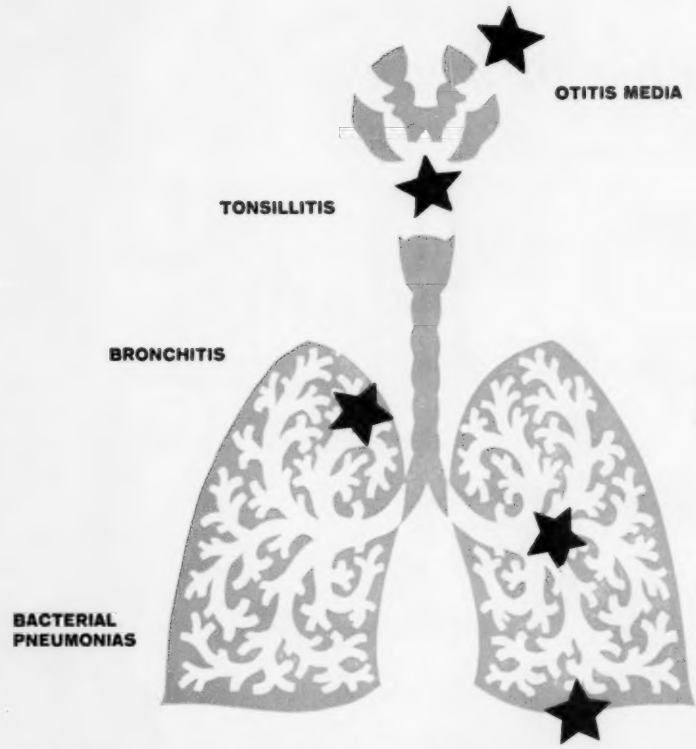

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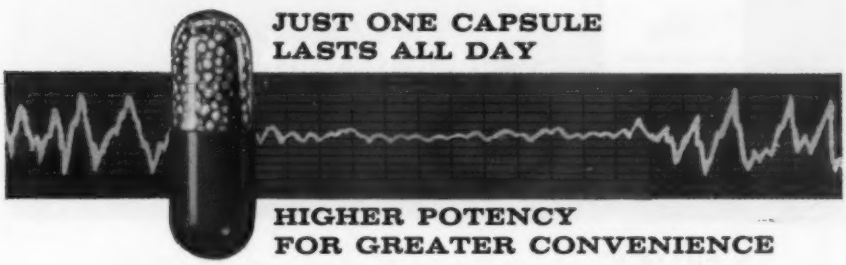

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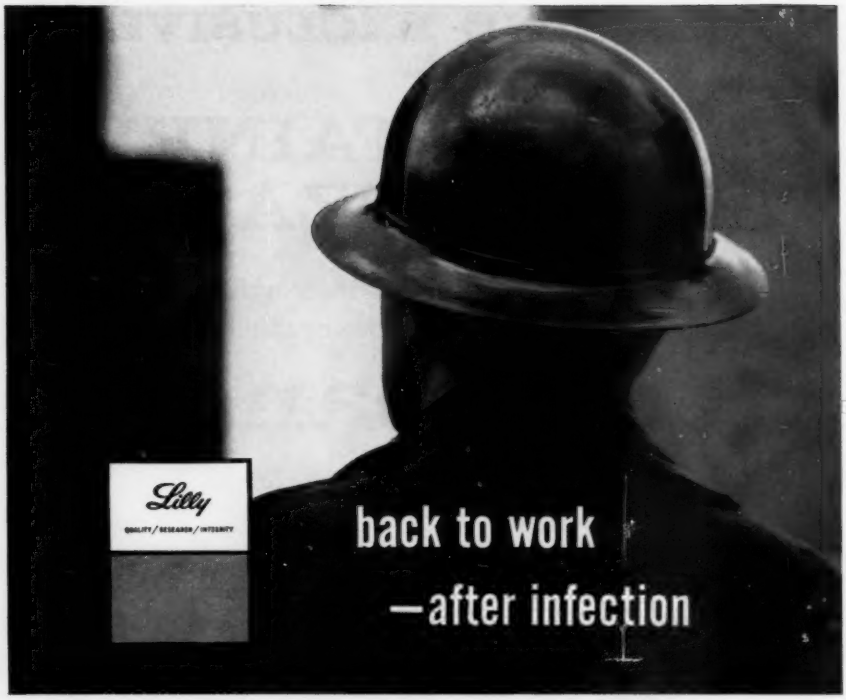

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 36, NO. 3 MARCH 1960

FACTORS INVOLVED IN CAUSING CONGENITAL MALFORMATIONS*

JAMES G. WILSON

Professor and Chairman, Department of Anatomy, College of Medicine
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BEFORE commencing to discuss the causes of malformations, I should like first to justify such a discussion by indicating the importance of malformations as a medical problem. The most direct way to do this is to mention some recent observations on incidence.

Estimates of the incidence of malformations have been variable and it is with uncertainty that one cites as the most reliable any of the several figures now available. The reasons for the lack of uniformity in reported rates become apparent when the various surveys are examined. In the first place, there is a considerable range of views as to what constitutes congenital malformations. Most writers agree that they are defects present at birth—hence congenital—but disagreement arises as to the meaning of the word malformation. Should its original and literal meaning be adhered to and the term applied only to anatomical defects that appear to be the result of aberrant embryonic processes, or should it be broadened to include functional and metabolic disorders, such as

* Presented at the Third Annual Postgraduate Week, *Research Contributions to Clinical Practice*, of The New York Academy of Medicine, October 6, 1959.

mental deficiency and the inborn errors of metabolism? Should all minor deviations from the norm be considered anomalous, or should an arbitrary criterion such as whether the defect in question is likely to cause clinical disease be set up? The answers to these questions can make a difference of several percentage points in the rate of malformations finally arrived at.

The sources of data upon which the stated rate is based may introduce further error. Information taken from death certificates is meager in the extreme and hospital records, although more voluminous, may be almost as uninformative. The attitude of the person making the diagnosis given in such records, that is, whether or not he has been alerted to look for the less obvious malformations, could account for additional variation in reported incidence. Regardless of the attitude of the diagnostician, the methods he uses are of great importance. Careful inspection will reveal the overt defects but radiography and other special techniques are required to uncover many hidden ones. The only method that approaches the absolute in revealing all congenital abnormality is, of course, postmortem examination. Any study on the incidence of malformations which does not include a high percentage of autopsies on individuals dying in the perinatal and infant periods must be considered incomplete. Finally, the validity of any survey depends on the age and survival status of the population being studied. This is well illustrated in the data compiled by McIntosh and associates (1954) presented in Table I. Ideally, figures on incidence should include not only the rates at stipulated times or in particular classes of subjects, but also cumulative rates in a representative population from birth at least through childhood.

Data that meet all of these qualifications are not available; nevertheless, there are studies which clearly indicate the magnitude of the problem. Gruenwald (1941), in doing 1131 successive autopsies at Cook County Hospital in Chicago on individuals ranging in age from premature infants to 89 years of age, found that 12 per cent of these persons had some anatomical anomaly. This figure is probably too high as an over-all rate of incidence. Gruenwald included such things as accessory spleens (14 per cent of his defects), which are regarded by many as normal variants rather than as anomalies. Warkany (1959) has estimated that at the present time 14 per cent of all infant deaths in the United States are directly attributable to malformations. But the deaths

TABLE I—INCIDENCE OF MALFORMATIONS IN RELATION TO SURVIVAL IN HUMAN OFFSPRING WEIGHING MORE THAN 500 GM. AT BIRTH

(Autopsies were done on 85.2% of stillborn and 86.5% of neonatally-dying infants)

Survival status	*Total deliveries*	*% malformed*
Antepartum death	81	13.6
Intrapartum death	30	23.3
Neonatal death (within 1st month)	98	29.6
Death between 1 and 12 months	17	70.6
Survival beyond 1 month	5,530	7.0

from McIntosh et al., 1954

do not tell the whole tragic story—what portion of the total human births yields defective individuals, regardless of when or how they die? The best data now available are those from the extensive prospective studies of McIntosh and his collaborators (1954). They reported a 7.5 per cent over-all incidence, including a one-year follow-up study of liveborn infants, as well as all infants dying in the perinatal period and all fetuses weighing more than 500 gm. A very significant incidental observation was that less than half of the liveborn infants with malformations (7 per cent of total) were diagnosed as being defective at birth. It can be argued that this study does not present a true picture on the grounds that, 1) it included previable abortuses, 2) most of the subjects were Puerto Ricans from the lower socio-economic strata, and 3) certain functional disorders not clearly developmental in origin (e.g., ptosis and nystagmus) were included. Remarkable confirmation, however, has been provided in a comparable prospective study recently made in Scotland by McDonald (1958). The latter reported a 3.8 per cent incidence at birth, which compares favorably with the incidence found at birth by McIntosh and associates. Such close agreement of rates in two somewhat different populations suggests that the mean incidence of malformations recognizable at birth must lie between 3.5 and 4.0 per cent. Those who feel that this is too high should consider the incidence of a single malformation, Meckel's diverticulum, which alone occurs in about 2 per cent of human beings. If the incidence detectable at birth doubles within the first year of life, as McIntosh and associates have observed, an over-all cumulative rate in excess of 7 per cent is readily acceptable.

Having thus emphasized that congenital malformations constitute a medical problem of sizeable proportions, let us now consider their causes.

Heredity. After the rediscovery in 1901 of the monumental work of Gregor Mendel it soon was realized that his laws of heredity had some applicability to man, as well as to plants and lower animals. It became apparent that not only the usual variations among human beings were often transmitted in a predictable way from parent to offspring, but also that certain defects were sometimes similarly transmitted. It was recognized that some of these defects were passed uninterruptedly from generation to generation by what came to be known as the dominant mode of transmission. Others were noted to occur in less regular succession, but nevertheless in such a pattern as to indicate that certain non-affected people were "carriers" of an abnormal gene, and that when two such carriers bred, approximately one-fourth of their offspring would be affected. The tendency of these abnormal genes to remain hidden until they occur in a double dose in the same individual accounts for their designation as recessive. Still other abnormalities were found to appear only in the offspring having the same sex as the affected parent, or occasionally in the offspring of the opposite sex as the affected parent, and are consequently said to be sex-linked. Fraser (1954, 1958) has compiled useful lists of malformations which are known to be determined by dominant, recessive, or sex-linked modes of inheritance.

New hereditary defects appear as a result of gene mutations. On the other hand, certain abnormal genes tend to decrease in the population as a result of their predisposition against marriage and parenthood, in other words, by negative selection. The rates at which these opposing influences, those causing new genetic abnormalities and those tending to eliminate them, are taking place in human populations are not known except in very general terms. Animal experimentation, however, has made one fact clear: the rate at which new mutations appear can be increased by exposing the germ cells to ionizing radiations. In a society such as ours in which we may expect increasing use, and perhaps also misuse, of radiations, it seems likely that the mutation rate of man will show a corresponding increase.

Although the lists of human defects that are regularly or occasionally determined by genetic means seem impressive, considered estimates are that not more than 10 per cent of all malformations have a clear-cut

genetic basis (Fraser, 1959).

Irradiation of the embryo. In addition to their actions on the germ cells in causing mutations, ionizing radiations may also act directly on the embryo to cause developmental defects. Radiations from two sources are known to have affected the human embryo, namely, therapeutic x-rays and the high energy emanations from atomic explosions. Many instances are on record of women having been subjected to massive radiation therapy for pelvic neoplasm during the early weeks of unsuspected pregnancy. Occasionally the irradiated embryos failed to be aborted and were carried to term as defective infants (Murphy, 1943; Glass, 1944). In these cases there is little doubt that the defects were the consequence of the irradiation because the organs primarily affected were the eye, the brain and, less often, the extremities, the same structures that are affected in the offspring of laboratory animals irradiated during pregnancy (Russell, 1949; Wilson, 1950). Although therapeutic irradiation of the pelvis in the presence of unsuspected pregnancy is unlikely, the fact that it has happened should alert every radiologist to the possibility. A woman in the reproductive years can be subjected to therapeutic pelvic radiation with relative safety only within two weeks following the beginning of menstrual flow. Only then can one be reasonably sure that a highly susceptible, early embryo is not present.

The other situation in which human embryos have been subjected to massive irradiation was in the atomic bomb explosions of World War II. At Hiroshima, microcephalic infants were born to seven of the eleven women in early weeks of pregnancy who were unshielded and within 1200 meters of the hypocenter (Plummer, 1952). At Nagasaki, 30 mothers within 2000 meters of the hypocenter showed major signs of irradiation and later gave birth to 13 infants who died in the perinatal period and to four children who were mentally retarded (Yamazaki et al., 1954).

Other physical agents have not been shown to be teratogenic in man but several have caused malformations in laboratory animals (Table II). It has recently been strongly intimated that hypoxia in early pregnancy may cause maldevelopment of the human embryo (Ingalls and Philbrook, 1958) but no real evidence for this has yet been presented.

Growth inhibitors and specific antagonists. To date, only one substance of this type has produced untoward effects, but this one

TABLE II—PHYSICAL AGENTS

In Man		
Radiations, therapeutic x-rays		Murphy, 1929; Murphy et al., 1943; Glass, 1944;
Radiations, atomic bomb blasts		Plummer, 1952; Yamazaki, Wright & Wright, 1954
In Experimental Animals		
X-rays	rat, mouse	
Hypothermia	hamster, chick	
Hypoxia	rat, mouse	
	rabbit, chick	(for references see
Elevated CO_2	rat	Kalter and Warkany, 1959;
Amniotic sac puncture	mouse	Wilson, 1959)

serves graphically to illustrate the hazard which these agents represent for the rapidly growing embryo. The folic acid antagonist, 4-amino-pteroylglutamic acid, because of the high mortality it produced in the embryos of pregnant animals, has been employed as an abortifacient in women. In pregnant women, as in animals, it has usually resulted in death of the embryos, but in at least six cases, human embryos survived the treatment and went to, or nearly to, term. All of these fetuses were highly abnormal (Thiersch, 1952; Meltzer, 1956; Warkany et al., 1959). Further use of these drugs as abortifacients constitutes obvious teratogenic risk, and if the search for effective cancer chemotherapeutic agents meets with any degree of success, growth-inhibiting compounds may come to be used extensively. The danger lies in their inadvertent use during early pregnancy. The inhibitors and antagonists that are now known to be teratogenic in experimental animals are shown in Table III.

Infections. The teratogenic property of rubella is too well known to dwell upon it here. The history of this agent, however, serves to remind us that a degree of restraint is in order when in the future new agents are found to cause malformations in man. It will be recalled that the early reports from Australia on the incidence of defective babies following maternal rubella ranged upwards to nearly 100 per cent (Gregg, 1941; Swan et al., 1946), whereas later surveys from other countries have shown much reduced malformation rates, now rarely exceeding 10 per cent (Greenberg, Pellitteri and Barton, 1957). The exaggerated

TABLE III—GROWTH INHIBITORS AND SPECIFIC ANTAGONISTS

In Man		
Aminopterin (folic antagonist)		Thiersch, 1952; Meltzer, 1956; Warkany et al., 1959
In Experimental Animals		
Nitrogen mustard	rat, mouse, chick	
Thiadiazole	rat	
Triazenes	rat, chick	
Other alkylating agents	rat	
Urethan	mouse	
Azaserine	rat, chick	(for references see
3-Acetylpyridine	chick	Murphy, Dagg and
6-Chlorpurine	rat	Karnofsky, 1957;
6-Aminonicotinamide	rat, chick	Wilson, 1959)
8-Azaguanine	mouse	
Thioguanine	rat	
6-Mercaptopurine	rat	
2-6-Diaminopurine	rat	

expectation that immediately followed the rubella discovery, however, served the useful purpose of causing more or less critical scrutiny of many viral infections during pregnancy. No others have been shown to be teratogenic.

One other infectious agent, the protozoan toxoplasma, may also affect the human embryo during development (Schwartzman et al., 1948; Feldman, 1958). The defects involve primarily the central nervous system, and although some of these are degenerative or pathological in nature, there is no doubt that others are developmental in origin.

Four infectious agents have caused malformations in animals and all are viruses (Table IV).

Hormone injections and endocrine conditions. On *a priori* grounds, hormones would appear to be likely suspect as teratogenic agents. Several of them readily cross the placenta and some may exist in fairly high concentrations in the maternal blood during pregnancy. The fact is, however, that only the sex hormones have been definitely implicated in man. Pregnant women have been given androgens for the treatment of such varied conditions as alopecia, sarcoma of the breast, etc. In several instances the male hormone was given in sufficient quantity at such an early time in gestation as to alter the genital differentiation of genetic

TABLE IV—INFECTIONS

In Man		
Rubella	Gregg, 1941; Swan et al., 1946; Ingalls & Purshottam, 1953; Greenberg et al., 1957	
Toxoplasma	Schwartzman et al., 1948; Feldman, 1958	
In Experimental Animals		
Influenza A	chick	
Hog cholera	pig	(for references see
Newcastle virus	chick	Wilson, 1959)
Blue tongue virus	sheep	

females, producing at birth female pseudohermaphroditism (Zander and Mueller, 1953; Grunwaldt and Bates, 1957; Hayles and Nolan, 1957). A similar outcome was recently reported following the use of synthetic progestins (Wilkins et al., 1958; Hayles and Nolan, 1959) and of stilbestrol (Bongiovanni et al., 1959) in the treatment of threatened abortion. Some of these progestins have been shown to have mild but unmistakable androgenic properties. Adrenal hyperplasia seems to have been ruled out in all cases. To produce the degree of masculinization described, particularly the fusion of the labio-scrotal swellings, it was necessary for the hormonal stimulus to have been present on or before the twelfth week of gestation.

The status of maternal diabetes in causing malformations has for some time been debated. Pooled data seem to indicate that anomalous infants are born to diabetic mothers about twice as often as to mothers in the general population, but, as has been pointed out by Rubin and Murphy (1958), such data probably contain a considerable bias. The perinatal death rate is much higher in the offspring of diabetic women than in those of non-affected women, and it is to be expected that more malformations would become known as a result of the larger proportion of autopsies performed on the former group. The role of the maternal diabetic state as a teratogenic agent thus remains in doubt.

It is of some interest in this connection that a diabetic state induced experimentally in pregnant mice with alloxan unquestionably causes malformations (Table V). Several other hormones have also been shown to be effective teratogens in laboratory animals, and it is noteworthy that these represent a considerable range of chemical structure.

TABLE V—HORMONE INJECTIONS AND ENDOCRINE DISORDERS

In Man		
Synthetic progestins	Wilkins et al., 1958; Hayles and Nolan, 1959	
Androgens	Zander and Mueller, 1953; Grunwaldt and Bates, 1957; Hayles and Nolan, 1957	
Stilbestrol	Bongiovanni et al., 1959	
Maternal diabetes(?)	Rubin and Murphy, 1958	
In Experimental Animals		
Androgens	rat	
Estrogens	rat, mouse	
Insulin	rat, rabbit, mouse, chick	(for references see Kalter & Warkany, 1959; Wilson, 1959)
Cortisone	mouse	
Vasopressin	rat	
Epinephrine	rat	
Alloxan diabetes	mouse	

Maternal dietary deficiencies. This category of agents has been widely studied in laboratory animals and much of the fundamental knowledge now available in the field of experimental teratology has been gained through such studies. There is, however, no proven instance of human malformation resulting from maternal dietary deficiency. The effects of starvation on human gestation were studied during World War II when conditions of famine existed in parts of Europe. Smith (1947) undertook a survey of infants born during and following the severe food shortage in Holland in 1944 and 1945. The most striking effect was a marked reduction in the number of pregnancies—it was estimated that 50 per cent of urban women became amenorrheic. No clear-cut effect was noted on abortion, stillbirth or neonatal mortality. Prematurity and congenital malformations were thought to be slightly increased, but the data were inconclusive because the total number of pregnancies was too small.

Under what were probably more drastic conditions of starvation during the siege of Leningrad in 1942, Antonov (1947) observed a considerable increase in the number of premature and stillborn infants. Children born during and following this period weighed an average of 500 gm. less than the normal average, and showed greatly increased morbidity in the neonatal period. No observations were made on congenital malformations. Thus, it seems that severe restriction of dietary

TABLE VI—MATERNAL DIETARY DEFICIENCIES

In Man		
none proven teratogenic		
In Experimental Animals		
Vitamin A	pig, rat, rabbit	
Riboflavin	rat, mouse	
Folic acid	rat, mouse	
Pantothenic acid	rat	
Vitamin B_{12}	rat	(for references see
Thiamine	rat	Kalter and Warkany, 1959)
Biotin	chick	
Vitamin D	rat	
Vitamin E	rat	
Starvation	mouse	

intake primarily affects the birth rate, which is sharply curtailed. There is no definite proof that the incidence of malformation is increased.

A clue to the failure of such generalized dietary deficiencies to affect embryonic processes is suggested in Table VI. A number of deficiencies have been found to be teratogenic in animals but most of them involved a specific vitamin. In each case an adequate diet was maintained except for the single deficient substance. With regard to this substance there was usually a delicate balance between the degree of deficiency which resulted in termination of pregnancy and that which permitted gestation to continue but under sufficient privation to cause malformation. Such a critically maintained deficiency of a single dietary component is highly unlikely to occur in human nutrition.

Advanced maternal age. It is well known that the occurrence of mongolism rises as the age of the mother at conception increases. Penrose (1939) has established on a firm statistical basis that the incidence doubles with every 5-year increment of maternal age after age 25. He also showed that certain central nervous system defects become more prevalent as maternal age increases. Davis and Seski (1948) in general confirmed these findings and noted that additional types of malformations occurred more frequently in the offspring of mothers past the age of 40 years than in the general population. It must be mentioned, however, that the prospective studies of more recent years have, except for mongolism, failed to show a correlation between advancing maternal

age and increased incidence of malformations.

Abnormal chromosomes. One of the most exciting developments in teratology in the past 15 years was the discovery that individuals afflicted by certain of the congenital syndromes possess an abnormal number of chromosomes. An extra chromosome making a total of 47 seems to be characteristic of mongolism (Jacobs et al., 1959). Some cases of Kleinefelter's syndrome also have 47 chromosomes (Ford et al., 1959[b]) and in these individuals the extra one is a female sex chromosome. A few persons with Turner's syndrome have been reported to have only 45 chromosomes, the missing one being the male sex chromosome (Ford et al., 1959[a]). It is too early to speculate on the extent to which chromosomal abnormalities may be associated with other congenital malformations. It is, nevertheless, already apparent that a new and unsuspected factor must be taken into account when considering the etiology of congenital diseases.

It was pointed out earlier that not more than 10 per cent of human malformations can be attributed to genetic causes. It should now be stressed that probably not more than 1 per cent can be attributed to all of the other causes combined, namely, physical factors, infections, growth inhibitors, endocrine states, and advancing maternal age. Thus, approximately nine out of ten cases of malformation in man are of unknown pathogenesis. Numerous examples in laboratory animals have been cited of malformations produced by all of the above classes of agents except advancing maternal age. Also teratogenic in animals are certain dietary deficiencies and a number of miscellaneous agents not discussed here (Wilson, 1959). Nevertheless, a degree of parallelism clearly exists in the matter of susceptibility to known teratogenic factors between man and the other animals. With full realization that the results of any one experiment cannot be extrapolated from animal to man, nor, for that matter, from one animal species to another, it is the conviction of this writer that a very promising approach to the problem of the causation of congenital defects in man is through animal experimentation.

This is not to say that the large-scale surveys of human pregnancies have not provided and will not continue to provide useful information. The numerous retrospective surveys have made substantial contributions; for example, they revealed that rubella and advancing maternal age were etiologic factors. The recent prospective studies have, for the

first time, provided a realistic estimate of incidence. But both of these methods have recognized limitations. The former requires that a particular entity occur with considerable frequency before a cause and effect relationship is recognized. The latter requires that the right questions be asked during pregnancy, if meaningful correlations are to be made with the condition of the child after delivery. Perhaps an intensification of experimental work with animals will provide the clues to cause and effect and to suggest the questions that need to be answered.

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SURGICAL ASPECTS OF MALABSORPTIVE STATES*

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THERE are many defects of gastrointestinal absorption which have surgical implications.

In a first group, the infirmity is due directly to operative interference and may be considered a proper price for the operative result expected, as in extirpation of cancers of the gastrointestinal tract, or may be judged fair exchange for relief of intolerable pain, as in some operations for ulcer. In some, malabsorption follows operation as an unexpectedly severe and troublesome complication.

In a second group, disturbances in gastrointestinal absorption are related to surgery because operative measures have been successfully used to correct the situation. And thirdly, defects may be amenable for treatment in the future by newer surgical techniques.

I propose to consider examples of each of these categories of gastrointestinal malabsorption: one, postgastrectomy difficulties, second, pancreatic inflammatory disease, and third, occlusive disease of arteries to the gastrointestinal tract.

When the stomach or any part of it is removed and continuity of the tract is reestablished by any one of several methods, normal function is sacrificed. Nutritional defects may follow the inevitable alteration in absorption of food. If the depression of absorption is not as profound as that produced by the original disease, peptic ulcer for example, the operation will be beneficial, in so far as the nutritional state will be closer to normal, but never actually optimum.

When the stomach is resected, the important reservoir function and mixing period are forfeited. This is a period of three to four and one-half hours' arrest of food in the stomach, during which time carbohydrates are rendered isotonic by gastric secretions, proteins are hy-

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drolyzed into shorter chained proteoses and peptones, and fat is stored so that it can be delivered beyond the pylorus in increments for which the duodenum is prepared. If secretory mucous membrane is reduced in quantity and the pyloric sphincter muscle excised, the disorders which may result are largely related to carbohydrate and fat content of the diet. Proteins can be managed satisfactorily without a period of gastric digestion. Carbohydrates ingested as hypertonic solutions, however, may cause trouble in the individual whose stomach has been wholly or partly removed. The task of secreting material to make solutions isotonic is then assumed by the jejunum, into which the concentrated material drops swiftly. Jejunal mucosa, being not well adapted for this purpose, withdraws fluid from the circulating blood volume as the stomach normally does, but without compensatory mechanisms which respond to gastric secretion. Hypotension, hyperperistalsis and an unpleasant sensation of weakness, the so-called dumping syndrome, sometimes follow. The complex mechanism of production of these symptoms as stated is oversimplified, but it is certain that loss of reservoir function of the stomach is implicated. Adaptation to the loss of natural homeostasis is, in most patients, satisfactory. New dietary habits learned by trial and error and feeding of isotonic carbohydrate solutions only, will relieve symptoms.

Proper digestion of fat is dependent on pyloric sphincter function and control of stomach propulsion. These are effected through contact of fat with duodenal mucosa and resultant secretion of the gastrointestinal hormone, enterogastrone. When a small increment of fat is delivered from stomach to duodenum, enterogastrone is secreted into the blood by cells in the duodenal mucosa. The hormone then brings about inhibition of gastric secretion, suppression of gastric motility and loss of gastric muscle tone. Only when fat is mixed with bile and pancreatic enzymes by the churning action of the duodenum and is passed on to the jejunum does enterogastrone secretion cease. Then stomach secretion, motility, and tonus resume, the pyloric sphincter opens and another increment of fat is delivered to the duodenum, and the cycle is repeated. Disorders of this exquisitely adapted system produce symptoms called fat intolerance, essentially a prolonged and exaggerated flaccidity of and retention in the stomach. When stomach and pylorus are removed, the system is destroyed. Inability to adapt to this sacrifice gives rise to most serious malabsorption states and nutritional disturb-

ances. The absolute fat intolerance and inability to gain weight post-gastrectomy are in all probability directly due to deliberate sacrifice of these processes. Adaptation to operative removal of functioning tissues is aided to some degree by restoration of continuity through anastomosing stomach directly to duodenum. This is the Billroth I operation, and it can be shown that immediate postoperative function of such patients is better than in those in whom continuity is reestablished by gastrojejunostomy or Billroth II. In the latter instance the duodenum is excluded from the circuit and is reconnected in side-arm fashion. Treatment of fat intolerance is feeding of small amounts of fat at frequent intervals, an imitation of gastric function. The inability of some patients to gain weight after gastric resection results from a defect which is not understood. There is no satisfactory treatment.

In the second category of malabsorption states, those which have been successfully managed by operative measures, is chronic pancreatitis. Here, repeated inflammatory attacks destroy the gland. Digestive enzymes manufactured by acinar cells become deficient in quality and quantity and with uninterrupted progress of the disease may be entirely absent. Hyperperistalsis of the small intestine, intractable sprue-like diarrhea, and malnutrition result. If the inflammatory attacks are prevented and scar does not imprison acinar tissue, the remarkable regenerative power of the pancreas can be invoked by careful dietary management.

In many instances, pancreatic inflammatory disease can be attributed to reflux of bile into pancreatic ducts through a common channel when resistance to flow is created by hypertonicity of the sphincter of Oddi. In some way the improper admixture of bile and pancreatic juice injures acinar cells, and trypsinogen is activated within the ducts. The precise conditions under which these events occur are not known. It can be shown by functional studies, however, that the sphincter of Oddi is a labile structure which is influenced by emotions, and that prolonged tonic contractions are harmful. It can also be shown that destruction of the sphincter mechanism by section of the muscle will prevent further reflux of bile into the pancreatic ducts. After this first step, the objective in treatment is to permit and encourage regeneration of injured cells. Careful dietary control and replacement of pancreatic juice by administration of potent extracts of the pancreas are essential. Progress in return of functional tissue can be followed by serial analyses

of pancreatic juice obtained through a duodenal tube after secretin stimulation of the gland. There have also been opportunities to observe such regeneration by microscopic examination of biopsy material after a lapse of time. The rate of regeneration varies, but could hardly be expected to be short of months and may take one or two years for complete restoration.

A third and most intriguing malabsorption state which relates to surgical endeavor is that brought about by occlusive disease of arteries to the intestinal tract. In a growing population of elderly people with arterial disease, this form of malabsorption is becoming more common.

While there are many similarities between intestinal and peripheral circulation, differences between the two are important in a consideration of disease. Blood entering abdominal arteries circuits through a portal venous system and enters veins with a large amount of its oxygen not extracted. Presumably, the high oxygen content of portal vein blood is for nourishment of the liver, since there is evidence that the liver can survive on portal vein blood alone. Oxygen saturation of portal vein blood varies, however, and is presumed to be due to varying rates of extraction by the intestine. In effect, the intestine has access to a large reserve of oxygen which can be extracted as function requires. Oxygen is needed by the intestine to provide for secretory activity, to maintain muscular tonus, and to permit segmental peristaltic activity. When these demands are minimal, the oxygen content of portal vein blood is high; when there is violent generalized intestinal activity, it is low. An important and not thoroughly appreciated side function of peristaltic activity is the pumping action of intestinal muscle which propels chyle with its absorbed fat through the lacteals and toward the thoracic duct.

In patients with occlusive disease, which cuts down arterial blood flow, all these functions are depressed, and a train of gastrointestinal symptoms associated with old age results. Loss of secretory activity is a subtle matter which causes ill-defined symptoms, including anorexia. Such loss is not easily recognized or measured and is probably the least disabling of the symptoms of arterial insufficiency. Loss of muscle tonus, however, results in distention of bowel and expansion of gas no longer compressed into a small volume. This is a common complaint of the elderly, and is commonly met by the sensible measure of not eating. With rest and adjustment of demands for oxygen, tonus will

return. In the meantime though, caloric intake is reduced and some nutritional defect can be anticipated. Serious complications of segmental distention can result, e.g., volvulus of the sigmoid colon. When intestinal peristalsis is inhibited by circulatory deficiency, symptoms are more severe: constipation progressing to obstipation, intestinal obstruction and a most important defect in fat absorption.

Because fat is absorbed almost exclusively as large particles through lymphatics and carried to the blood stream through the thoracic duct, there is early disability when peristalsis is inhibited. Flow of lymph in lacteals is dependent on the pumping action of intestinal muscle contraction. The elderly individual with arterial occlusion first becomes intolerant of fat in the diet, then mobilizes fat stores throughout the body for metabolic purposes. Exhaustion of these stores creates the characteristic wrinkled skin and withered appearance of advanced old age. Complete deprivation of fat in the diet is tolerated for remarkably long periods, and there is great danger in forced feeding as a therapeutic measure. Just as overexercise of the ischemic limb can precipitate gangrene, a forced fat meal can make demands on a precarious circulation and cause gangrene of the intestine.

It is just such catastrophic events which have emphasized the importance of early symptoms. In a few individuals surgical attack on the occluded mesenteric vessels by endarterectomy has succeeded in restoring sufficient circulation to bring back a pink color to a black ischemic intestine. Unfortunately, such good results are unusual, but new techniques of endarterectomy, small vessel anastomoses and prosthetic vessel replacements are increasingly encouraging.

Elderly people make remarkably good dietary adjustments to their disabilities and not infrequently overzealous family or medical advisors are the culprits in calamitous obstructions, volvulus or so-called mesenteric thrombosis. When an old person decides, on his own, that he will not eat fat, that his meat intake will be scanty, that he wants small frequent feedings of carbohydrates, sometimes only candy, he is adapting to circulatory deficiency. Carbohydrate is the most easily absorbed source of calories, and he may be keeping himself alive by such a course. The hospital dietician should not insist on a balanced diet of three meals a day, because one such meal may cause complete failure of what little circulation remains in the intestine.

The future should bring increasingly frequent attempts to restore

circulation in mesenteric vessels at a time before impending gangrene forces the surgeon to perform more radical procedures. Emergency operations under such circumstances are not likely to succeed because the technical requirements are so exacting. It is possible at this time to delineate the extent of mesenteric vessel occlusion by aortography. On the basis of such findings, a carefully planned and executed operation might well restore good function, proper absorption and optimum nutritional status. The leading information pointing to intestinal arterial insufficiency is the symptom complex of anorexia, bouts of distention, increasing constipation and, most important, obstinate dietary foibles which seem irrational.

Three specific disturbances in intestinal absorption have been considered. All have some relationship to a surgeon's activities and therefore might be termed "surgical". In one, the surgeon brings about the malabsorptive state, perhaps by intention and perhaps not. The point is that removal of any part of the intestinal tract or rearrangement of its sequential secretion and absorption pattern will inevitably require adaptation to an abnormal situation. In the second, treatment of severe disease, pancreatitis, may be initiated by a surgical maneuver. In the third, the future promises much for the application of new techniques in vascular surgery for the relief of occlusions in intestinal arteries.

RECENT CONTRIBUTIONS TO THE UNDERSTANDING AND TREATMENT OF BLADDER TUMORS*

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THE CLINICAL TREATMENT of vesical neoplasms is such as to invite critical comment from the uninitiated. Although we urologists regard the most innocuous-appearing papillary tumors as likely to recur and hence potentially malignant, we treat bladder tumors by methods which might be regarded as rather conservative, if not ineffectual. These treatments consist of electrodesiccation and transurethral resection. Not until the tumors become multiple and impressive by virtue of number, or obviously invasive and no longer subject to surface treatment, do we resort to extirpation. Often we then remove only part of the bladder, a circumstance rarely recommended, for example, in surgical removal of tumors of the prostate or lung.

Are there mitigating circumstances which justify these practices? There are and there are not. The cure rate for bladder cancer is low indeed, if one speaks of ultimate cure, not five-year survival. Why then do we not treat early cases by more adequate radical means? No doubt the lack of a suitable physiological substitute for the urinary bladder prompts us to continue present practice. The few remarkable cures each of us has seen to follow conservative surgery lead us to hope for more. Perhaps the morbidity and the mortality associated with radical surgery and its complications deter some urologic surgeons from radical extirpation when the lesion is curable.

The magnitude of the problem can be appreciated when results in a large series of unselected patients are critically evaluated. Franksson's series of 434 cases, embodying all the usual techniques, shows that recurrences are prevalent: after endoscopic coagulation, 57 per cent; after transurethral resection, 77 per cent; transvesical coagulation, 83

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per cent; partial cystectomy, 59 per cent. After cystectomy, 70 per cent did not survive one year. X-ray therapy cured only 14 per cent.

Whitmore has recently summarized his results following 160 radical cystectomies, of which only 18 per cent survived five years. But of patients with multiple superficial tumors or with rapidly recurring tumors, 44 per cent survived five years after cystectomy. These results led him to conclude that the most important factor in survival was not the type of treatment employed. Survival was determined by the nature of the tumor.

Higgins' results were quite similar. However, if only the tumors which did not extend outside of the bladder are considered, and deaths from causes other than cancer are excluded, the five year cure rate increased from 33 per cent to 61 per cent.

Morrison's study of early results after x-ray therapy using eight million volts showed that 24 per cent survived two years. It seems possible that cystectomy could cure bladder cancer, were it performed early enough. Unfortunately, the morbidity and the late mortality associated with conventional methods of urinary diversion, to say nothing of the rather poor physiologic functioning of substitutes available for total bladder replacement, make total cystectomy unattractive. Critical examination of the results of clinical management of vesical neoplasm leads me to the conclusion voiced by Jewett in 1945: "During the last 25 years a variety of procedures for the treatment of infiltrating carcinoma of the bladder have been reported, and in general the results have been disappointing."

The questions arising from these considerations are:

1. Is there something peculiar about transitional tumors of the bladder which sets them apart from other carcinomata?
2. Is there something peculiar about patients who have transitional tumors that tends to make transitional tumors recur?
3. Is there something peculiar about the urological attitude toward treatment?
4. Are there peculiar needs for knowledge and techniques the absence of which is responsible for the lack of improvement in the results obtained with our present methods of treatment?

Let us turn our attention to the tumor. Following the reports of the accidental human experiments in England and the United States that implicated chemical agents as causes of bladder cancer, there has

been an unusually great amount of experimental work done in this area. Based upon these researches, the following facts hold for *induced* transitional cell tumors:

1. An induction time of about 20 per cent of the life span of the species is necessary: human, bovine, dog (Scott, Williams; Pamukcu, 1955, Hueper, Wiley and Wolfe).
2. The intensity and duration of the carcinogenic stimulus may alter induction time (Scott and Williams, McDonald and Lund).
3. Only those species which excrete the carcinogen in the form of free ortho-amines develop bladder tumors: man and dog, but not rabbit or rat (Boyland, Harris and Horning; Bonser, Bradshaw, Clayson and Jull). In this sense the induction of neoplasms of the bladder is metabolically conditioned; but Twombly could not distinguish a qualitative difference in the excretion products of C-14 Beta-naphthylamine.
4. The conjugated carcinogen in the urine is reabsorbed by the mucosa of the bladder, possibly after enzymatic liberation of the active carcinogen (Boyland, Wallace and Williams). In all animals and humans bearing induced bladder tumors, substances are present in the urine which can be demonstrated to be carcinogenic. Even in patients not known to have been exposed to carcinogenic substances, the urine can be found to contain substances which produce neoplastic changes. This is in contrast to the urine of normal people or patients afflicted with carcinoma of other organs (McDonald, Hill and Dermanis). Table I: It is interesting to note that the most potent extract is the benzene extract which does not contain the tryptophan metabolites or conjugated naphthols heretofore considered the most likely tumor-inducers (Boyland and Williams; Twombly).
5. Human and animal tumors can be observed to undergo an orderly progression from submucosal telangiectasis, metaplasia, papilloma, and papillary carcinoma to sessile invasive carcinoma (Gay; McDonald and Lund). In man and dog, the vascular component is minimal, but in bovines, 75 per cent have mixed angioma and carcinoma (Pamukcu).
6. Once the papilloma stage is reached, no further carcinogen need be given to permit growth and progressive dedifferentiation of the tumor (Scott and Williams; Hueper).

TABLE I—EXPERIMENTAL TOPICAL CARCINOGENICITY OF EXTRACTS OF HUMAN URINE SOLIDS TO THE URINARY-BLADDER POUCHES OF RATS

Solvent Extract	*Carcinoma Bladder*		*Normal Males*		*Extra Urinary Carcinoma (lung, G. I.)*	
	Tumors	*Pouches*	*Tumors*	*Pouches*	*Tumors*	*Pouches*
Benzene	4	9	0	13	0	7
			0	7		
N-Butanol	2	7	0	7	0	5
			1	8	0	4
Tert. Butanol	2	8	0	5	0	10
			0	8	0	11
Residue	1	6	0	6	0	5
					0	4

7. Once developed, the majority of human tumors and all animal tumors do not depend upon substances in the urine for continued growth, a few clinical reports notwithstanding (Abeshouse and Scherlis; McDonald and Lund).
8. Indeed, tumor implants to new locations in the urinary bladder or prostatic urethra, or in the perivesical tissues in humans and homotransplants in animals, establish the transitional papillary carcinoma as an aggressive invasive malignancy, even in its most innocuous-appearing form (Franksson; Hinman; McDonald and Thorson).

We should next consider areas of conflicting experience with induced experimental and spontaneous clinical transitional cell tumors.

1. The majority of spontaneous tumors are single. Induced tumors are usually multiple, whether in humans or animals.
2. Dietary factors seem to be of no importance in humans; but, at least in the acetaminofluorene-induced tumors in animals, the level of dietary protein and tryptophan is definitely related to tumor incidence (Dunning, Curtis and Maun). In cattle, dietary factors have been implicated but not established (Pamukcu).
3. Enzymatic alterations are reported in humans. Urinary-glucuronidase levels are reported to be higher in patients who have recurrent bladder tumors (Boyland, Wallace and Williams).

It is suggested that this enzyme may hydrolize the conjugated carcinogens, thus rendering them available for absorption by the bladder mucosa which responds with neoplastic change. No changes in the glucuronidase activity of the urine of animals undergoing vesical-neoplasm induction have been observed.

4. It is suggested that the concentration of the urine may have some importance, since one series of patients with bladder cancer contained an unusually large proportion of poor water drinkers (Wallace). Bovine bladder tumors have been observed to appear more frequently following a dry summer (Pamukcu). No observations on the effect of urinary concentration in dogs have been noted, but the concentration of naphthylamine in the urine is 200 times that of the blood (Bonser, Clayson and Jull, 1951), and reabsorption would no doubt be favored by high concentrations of urinary carcinogens.
5. Abnormal metabolism of tryptophan has been found to be associated with bladder cancer in humans (Brown and Price). The majority of patients with transitional tumors excrete quantitatively more of the carcinogenic agents: acetylkynurenin, hydroxykynurenin, and kynurenic acid. They also respond to a tryptophan load by excreting three times more of the abnormal tryptophan metabolites than do normal humans. Administration of pyridoxine, vitamin B_6, to bladder-cancer patients normalizes their metabolism of tryptophan. There is no evidence that the bladder tumor patient is deficient in pyridoxine, but results of tryptophan metabolism studies suggest that there is an increased need or utilization of B_6.
6. Human bladder tumor cells have never been observed to contain virus inclusion bodies; they grow rather indifferently in tissue culture and have, so far as I know, not been grown in animals. The Hughes and Lewis mouse bladder tumor are readily transplanted to any strain of mouse, but not by ultrafiltrates. Recently, the Shope rabbit ear papilloma virus has been reported by Satter to produce vesical papillomata when filtrates are injected into the bladder mucosa.

With these data in mind, how can we answer our questions?

1. Is there something peculiar about transitional tumors of the bladder which sets them apart from other carcinomata? There

are several peculiarities of bladder tumors. They may be initiated by resorption of carcinogenic substances excreted in the urine. They give early warning to the patient, usually by gross bleeding. They tend to recur either by implantation or *de novo* and become progressively more malignant with time.

2. Is there something peculiar about species who form bladder tumors? There is. Exogenous chemicals must be metabolized to carcinogenic metabolites, or no tumors will develop. In humans not exposed to known precursors of carcinogenic metabolites, there is converging evidence that those who form bladder tumors are metabolically and enzymatically distinguishable. They excrete substances which induce tumors in susceptible animals, whereas normal humans do not.
3. Is there something peculiar about the current urological attitude toward treatment? Yes, there is. Although we know that 86 to 100 per cent of the tumors in Jewett's Groups B and A are potentially curable, a high incidence of recurrence *in situ* or of new tumors can be expected after conservative treatment; yet we are reluctant to perform cystectomy, unless it is forced upon us as a last resort. Until some specific chemotherapeutic method is found, however, the only dependable treatment is cystectomy.
4. Are there peculiar needs for knowledge and techniques, the absence of which is responsible for the lack of improvement in treatment? Yes, there are. Although we obtain much help from the gross and microscopic classification developed by Marshall, additional methods are needed to help determine which tumors will be apt to recur, and hence need more energetic treatment. By means of tissue culture techniques, we have attempted, unsuccessfully, to establish the degree of malignancy of bladder tumors. Although a number of tumors grew well for several weeks *in vitro*, there was only slight correlation between growth *in vitro* and the clinical course of the patient. Additional study of the tumors *in vitro* may be helpful in establishing the biological potential of the tumor. Because of the tendency of bladder tumors to implant, especially to traumatized bladder mucosa, we need some form of chemoprophylaxis against implantation of tumor fragments liberated at the time of transurethral resection and fulguration. This was recognized at the turn of the century

and brought again to our attention by our laboratory studies in dogs and Hinman's clinical observations. Many suggestions are to be found in the literature on this subject. Resorcinol, ethyl alcohol, silver nitrate, 50 per cent phenol in glycerine, trichloracetic acid, and chlorpactin, all have at one time been advocated.

McDonald and Hill recently completed a preliminary study of the effect of 25 chemical, antibiotic, and carcinostatic agents in an *in vivo* testing-system, which in many ways duplicates the clinical situation. The method derives from the observation of Wallace and Hershfield that Walker 256 tumor fragments injected into the bladders of rats via the ureter implanted and grew in the urinary bladder. Of 142 untreated control animals used in our experiments, 97 per cent had one tumor and 70 per cent had two or more tumors in eight days. The largest tumor often filled the bladder and frequently measured 7 mm. in diameter. Several treatment methods were used to assess the merit of the substances as tumor sterilizing agents.

Method I: tumor cells were pretreated with the agent for five to ten minutes, then implanted.

Method II: tumor cells were injected into the empty bladder and immediately thereafter the bladder was filled with the test solution for three minutes.

Method III: tumor cells were injected into the bladder, and systemic treatment was given for seven days.

Method IV: tumor cells were implanted. Four days later, the bladder was filled with test solution for five minutes.

Methods I to IV become increasingly more demanding of the chemoinhibitor. Actually, Method IV is a test of chemotherapy rather than chemoprophylaxis. Criteria of merit were absence of tumor in ten or more implanted rat bladders on the eighth day after implantation. Of the chemical agents tested by Method IV, none gave any significant protection against tumor development. Those chemicals included sodium chloride, carbonate, citrate, and sulfate, chlorpactin and phenol. Fifty to 70 per cent of the animals were protected by one topical treatment with penicillin and streptomycin, chloramphenicol, neomycin and tetracycline. A number of known tumor inhibitors were also tested. Podophyllin, auramine O, colchicine, actinomycin D, nitrogen mustard, Beta propiolactone, chlorambucil, and urethane gave less than 50 per cent cures. Diethylene phosphoramide gave 60 per cent cures. Triethy-

lene thiophosphoramide gave 67 per cent cures. Triethylene melamine gave 60 to 100 per cent cures.

As a further test, we studied the anerobic and aerobic glycolysis of the Walker 256 tumor and human bladder tumors. With the exception of podophyllin, to which the Walker 256 tumor is more sensitive *in vitro*, the human and rat tumors responded similarly to topical treatment with the carcinostatic agents. The most effective *in vitro* inhibitors of human bladder tumors were, in decreasing order of effectiveness, triethylene melamine, auramine O, nitrogen mustard and sarkomycin. Not all of the agents could be tested on human bladder tumors.

Conclusions of the *in vitro* and *in vivo* preliminary testing suggest that TEM and thio TEPA are the two substances most worthy of future study. A note of caution concerning the instillation of these substances into the urinary bladder should be interjected, since we know that TEM can be absorbed from the dog bladder, with subsequent suppression of the bone marrow.

It is quite possible that a practical method of chemoprophylaxis or chemotherapy of bladder tumors may be developed. One advantage which favors this is that high concentrations of a suitable chemoinhibitor could be instilled into the bladder for treatment of superficial tumors. Intrinsic radiation may be possible, for Bunce has found that P_{32} will localize in bladder tumors.

In order to better the lot of the patient who survives after therapeutic cystectomy, better methods for total bladder substitution with urethral voiding are needed. Ureterosigmoidostomy, a hydraulically and physiologically unsound procedure, frequently complicated by renal sepsis and failure, is soon to be abandoned. The ileal urinary conduit and rectal bladder with proximal colostomy are much happier compromises. But experience with total bladder substitution by segments of sigmoid anastomosed to the urethra is accumulating and may lead to wide use of this potentially more acceptable form of urinary diversion. Gil Vernet has reported good results in 60 cases. In two patients we found considerable difficulty with mucus obstruction of the urethra and poor voiding, which has led us to delay further similar procedures, pending a satisfactory solution to this problem. In animals, total colon-bladder substitutes function well, as reported by Scott and Boyd, and have the advantage of resistance to carcinogenic agents. We have observed that the permanent destruction of the colon mucosa is difficult

to achieve surgically and chemically. X-radiation can destroy the colon mucosa, leaving it to be replaced by transitional epithelium, but x-rays also lead to fibrosis of the muscle wall with marked reduction in capacity. We hope to evaluate B-irradiation in canine colon bladders in an endeavor to decrease the mucus production. Although Weinberg, Sinatra, and Vasquez have shown marked atrophy of ileal mucosa after prolonged contact with the urinary stream, colon bladders behave differently with respect to mucus production. Our two patients continued to have difficulty during the entire period of observation, which extended for two years in one case and two and a half in the other.

If better methods of total bladder substitution can be developed, total cystectomy can be performed early in the course of multiple superficial, invasive, or rapidly recurring tumors without hesitation on the part of the surgeon or undue suffering on the part of the patient. Specific chemotherapy or chemoprophylaxis may be forthcoming and supplant radical surgery, but cystectomy during the stage at which the tumor can be encompassed is our only hope for cure of the invasive or rapidly recurring vesical neoplasm at this time.

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MANAGEMENT OF SURGICAL CONDITIONS OF THE ALIMENTARY TRACT IN INFANCY

*Transcription of a Panel Meeting on Therapeutics**

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MODERATOR GEORGE H. HUMPHREYS: The subject of our discussion is *Management of Surgical Conditions of the Alimentary Tract in Infancy*: This rather heavy title was an attempt to put into scientific language the proposition, "what to do about a vomiting baby", and particularly what to do about a vomiting baby in whom the doctor suspects, but is not sure, that a surgical problem may be present, how to determine whether a surgical problem is present, what sort of problem it may be, and what the implications of this problem are.

I shall ask Dr. Hodes to begin the discussion by commenting on the problem presented by a vomiting baby, from the pediatrician's point of view.

DR. HORACE L. HODES: I shall start first with the consideration of vomiting in the newborn period which, diagnostically, it seems to me, gives the pediatrician the most difficulty.

In defining vomiting, I am talking about something more than the small amount of regurgitation which the newborn infant frequently exhibits, and which is usually without pathological significance. It takes some experience on the part of the doctor to know at what point this has been exceeded. If there is repeated vomiting, in the newborn period particularly, this must be regarded as a potentially very serious symptom and the cause for the vomiting must be looked for. There are causes outside of the gastrointestinal tract, which I will dispose of very briefly.

First, we know from dealing with many infants in the newborn period, that a labor which has been prolonged and attended by hypoxia in the infant is quite likely to be followed by a period of vomiting. In general, the baby may do some vomiting after difficult labor. Similarly, intracranial injury is one of the important causes of vomiting in the newborn period. Other causes include tetany of the newborn and septicemia of the newborn – septicemia that may be due to many different organisms, but all producing a similar clinical picture. In these conditions vomiting is often a prominent symptom.

Again, I should like to mention that babies born with a serious kidney anomaly or anomalies, in addition to an infection, may exhibit vomiting, just as they do in later life.

However, whenever we believe that vomiting of the nature described is present, obstruction of the gastrointestinal tract must be considered and must be excluded. The point that I am trying to emphasize is that there are many gastrointestinal causes for vomiting which must

be considered, and I shall mention some that come to mind. I am sure the surgeons will discuss these causes in much greater detail. Atresia of the esophagus worries the pediatrician. We like to exclude this in all babies whom we see. As you know, this is not really vomiting but rather regurgitation. The material never gets to the stomach and this condition can easily be excluded by passing a catheter into the stomach – it is one of the first things that I have in mind when I see a newborn baby. Another important cause of vomiting is congenital atresia of the small intestine. This may be in the nature of a diaphragm or blind-sac arrangement, with the obstruction (usually) below the ampulla of Vater. In these cases, the vomiting frequently contains bile. The most common site of atresia of the small intestine is in the ileum, with the duodenum next, and then the jejunum, in order of frequency.

Colonic atresia is relatively rare. Clinically, the baby may or may not exhibit much evidence of obstruction, which is a point that has been brought home to us on many occasions. Whenever we suspect obstruction of the gastrointestinal tract, we obtain a "flat" x-ray film of the abdomen, which, again, I believe the surgeons will discuss with you in more detail.

In addition to atresia, congenital stenosis of the small intestine is a possibility. Here the duodenum is the most common site, with the ileum next, and the jejunum following.

We also think of meconium ileus, particularly if there has been a family history of cystic fibrosis of the pancreas. Here, again, the x-ray of the abdomen is valuable, for it can materially aid in making the specific diagnosis by actually revealing a granular kind of meconium in the x-ray itself. Occasionally there has been perforation with accompanying peritonitis and calcified meconium lying loose in the abdomen.

Malrotation of the intestine is another possibility that must be considered in thinking of intestinal obstruction in the newborn period. This obstruction usually involves the duodenum, being due to bands, or, in about half of the cases, to midgut volvulus duplication of the intestine. Duplication of the intestine is another condition which may lead to intestinal obstruction. On rare occasions, this anomaly may cause obstruction in the early stage of life because the duplicated intestine may be large and may press on one of the other segments of the intestine. Duplication usually affects the small intestine. Very rarely do we see other obstructing anomalies, such as that caused by annular pancreas, an ex-

tremely rare occurrence. Vomiting may also result from an imperforate anus which has been overlooked. In these cases, vomiting may occur as a late symptom. In almost all instances, this condition is discovered long before vomiting occurs.

This exhausts the list of things that come to mind as causing obstructive symptoms in the first few days of life. Pyloric stenosis usually belongs in the period after the first week of life, so that we do not ordinarily think of this condition during the first day or two of life. The same is true of intussusception which comes on later in infancy, the peak incidence occurring between the age of three months and two years.

To sum up, then, some experience is required in the newborn period to make the physician recognize the pathologic significance of vomiting. We should be aware of causes outside of the intestinal tract; but when we suspect that the vomiting is of pathological significance, we must exclude obstruction of the intestinal tract.

MODERATOR HUMPHREYS: Dr. Hodes has mentioned many different conditions without telling us too much about any one, because he indicated that he expects the surgeons to consider them in greater detail. He has begun at the mouth and systematically worked down to imperforate anus, and we shall do the same in the surgical discussions prior to questions, at which time we need not be quite so systematic.

I shall therefore ask Dr. Richardson to speak on conditions related to the esophagus which are associated with need for surgery in infancy.

DR. WILLIAM R. RICHARDSON: Had Dr. Humphreys not emphasized that this panel is primarily concerned with the problem of vomiting in the infant, my own portion of the assignment would, nevertheless, have been predominantly one of discussion of obstruction because the function of the esophagus is almost exclusively one of transport.

The lesion with which I shall spend most of my time is well known but is still sometimes considered mysterious and incurable – congenital esophageal atresia with or without a tracheo-esophageal fistula.

(Slide) This is a diagram demonstrating the various types of anomalies of the esophagus. It gives the posterior view at autopsy, showing the blind esophageal pouch at its termination high in the mediastinum and below is the distal esophageal segment connected by a fistula to the lower trachea just above the carina. This is the usual site of the fistulous connection; involvement of the right main bronchus is second in fre-

quency.

(Slide) A lateral view shows the anatomy of the most common type, which fortunately is encountered in about 85 to 90 per cent of the infants with this anomaly. Sometimes there is no cord between the two segments, but usually a few fibers of muscle and a little fibrous tissue are found. The blind esophageal pouch is nearly always thick-walled and hypertrophied. The thoracic level varies slightly, about T-3. In order to help identify this pouch at operation, it is sometimes necessary to have the anesthesiologist push down a small tube and it can be seen to descend to two or three vertebral levels. The connection of the distal esophageal opening with the trachea is illustrated here, and my own impression is that, although it is usually smaller than shown here, it may vary and sometimes can be very troublesome when it is quite large. Occasionally there are associated anomalies of the trachea of other types. Here is a case of atresia without a fistula. This occurs in approximately 5 per cent of cases.

(Slide) This is a very rare type with a fistula to the trachea from both the proximal and distal esophageal segments.

The next slide illustrates the congenital tracheo-esophageal fistula without atresia, and the following slide shows a congenital esophageal stenosis. In this last slide, it should be noted that the level of the esophageal lesion is somewhat lower than the common atretic level. That is something to remember.

Regarding the question, "How common are these lesions?", I think Dr. Humphreys, in a recent article, quoted 1 to 3,000 as the incidence at Sloane Hospital. It is difficult to determine exactly, but if one examines any of the series of cases reported from various medical centers where the operation is carried out fairly frequently, the numbers have gradually increased to a degree indicating that many hospitals average one or two cases per month. I know that this is still considered a rare condition, but when one contemplates a possible life expectancy of 70 years for these infants, salvage becomes tremendously important.

It is more important that we stress the problems of early diagnosis, preoperative management, and the factors that influence prognosis, rather than the various technical surgical aspects. The diagnosis itself should be easily made. This is especially easy for the surgeon to say since the diagnosis is usually made before he sees the baby. If, at the time of delivery and during the first few hours after birth, the possibil-

ity of the presence of this lesion were considered in all newborn infants who have respiratory difficulty, who breathe poorly, who have excess mucus or saliva, who froth at the mouth or drool, and who have choking or cyanotic spells, there should, in my opinion, be no difficulty in making the diagnosis even before the first feeding. Meticulous observation is required and, again, as Dr. Humphreys has emphasized, it is mandatory that we doctors, if we cannot be there to observe, must train the nurses to observe closely and record accurately. Reading the nurse's notes is generally of much more importance in pediatric than in adult surgical practice. In other words, we need to be both alert and suspicious, and if, when cause for suspicion arises, action follows, then I think the correct, early diagnosis will be forthcoming in many more cases. I can hardly overemphasize the importance of educating the nursing and attendant personnel connected with the areas of our hospital, concerned with perinatal care.

Certain diagnostic clues that may add to our index of suspicion are:

1. Prematurity: About a third of the infants with this lesion are born weighing less than 5½ pounds, and only about 10 or 15 per cent weigh more than 7 pounds.

2. The occurrence of *hydramnios* in the mother should arouse suspicion and should result in further diagnostic study. About 10 or 15 per cent of the mothers are found to have hydramnios. We don't have good reverse statistics, but certainly the infant born of a mother with hydramnios, especially if without obvious cause, or arising somewhat acutely in the third trimester, should undergo further specific diagnostic procedures, including attempted passage of a catheter and x-ray studies. It may well be that the hydramnios, which I am sure Dr. Santulli and Dr. Hiatt will cite as important in the maternal history when obstruction occurs further down in the upper intestinal tract of the infant, can be a cause of premature labor.

3. If an infant is born with one major or minor congenital anomaly, associated anomalies are sufficiently common for us to be on the lookout for a second, and of the major anomalies the esophageal ones seem to have an accompanying defect more often than most. About one-third of the babies have associated anomalies, sometimes multiple, often serious or fatal.

I remember well two infants admitted with imperforate anus as the only major diagnosis. On one I was called by the nurse at two or

three a.m. She did not describe the symptoms. She just said, "Dr. Richardson, I think baby Jones has an esophageal atresia." This was a bit humiliating. I had been sufficiently impressed with the blind bottom to let it go at that, but she was a graduate nurse who had taken care of 40 to 50 esophageal atresias and certainly knew much more about it than I did. By then, I had learned not to disregard her opinion and we confirmed the diagnosis promptly. Beware of the baby with the imperforate anus – who drools!

4. Other conditions that should arouse suspicion: *Right-upper-lobe* pneumonia or atelectasis should remind you that aspiration has a predilection for this lobe, and such a finding in a newborn baby should mean esophageal atresia with fistula, until ruled out.

5. Rapidly developing marked *abdominal distention* is rare in infants and one thing that can precipitate it is atresia with a large fistula.

Other signs and symptoms will usually be apparent. Later diagnostic indications are feeding difficulties, pneumonia, and actual expectoration of blood-tinged material. I have been impressed by the number of late-diagnosed cases which present, among other things, sclerema neonatorum.

The diagnostic steps that should be carried out are simple. The first and simplest is the attempted passage of a catheter. It is important to use a new, fairly stiff catheter, a red rubber urethral No. 8 or 10 French, lubricated and passed through the nose. Normally, it should pass easily into the stomach, and if it meets an obstruction at 10 to 15 cm., usually nearer 10, the diagnosis is practically made.

In my experience, auscultation of air injected into the stomach has always appeared to be foolproof, but only three or four years ago I attended an autopsy at the Boston Children's Hospital where the diagnosis of esophageal atresia had been missed. The resident had suspected this condition and had passed a catheter, had passed air into the catheter with a stethoscope on the abdomen, and, being sufficiently convinced that air was heard bubbling right under the scope, treated the infant, without further x-ray studies, for right-upper-lobe pneumonia.

This and one other case have convinced me that, if there is the slightest question or doubt, fluoroscopy is necessary as a check against curling or defect of the catheter.

Whether radiopaque dye should be injected is debatable. My personal preference is to use it. Were I certain that I would refer the patient to another physician for definitive therapy, I would not only

not inject Lipiodol (and under no circumstances, barium) but would leave therapy entirely to him. If Lipiodol is used, only about 0.5 ml. should be injected through a catheter with a hole at or very near the end. Then snap the PA and lateral films and immediately aspirate the catheter to avoid flooding the infant.

I wonder—and this might be a question for discussion—if we should, as has been suggested intermittently for a number of years, attempt to pass a catheter into the stomach of all newborn babies. I believe that at present the only babies that routinely undergo this procedure are those delivered by cesarean section. Is that right, Dr. Hodes?

DR. HODES: Yes, that is correct.

DR. RICHARDSON: There are many drawbacks, yet I keep seeing cases that, I believe, might well have been salvaged. It is true that one need not pass the catheter routinely if all babies are observed closely when the first stools are passed, and checked for excessive mucus and green vomitus. With such careful observation, the routine use of the tube may be somewhat meddlesome.

The question of where the definitive therapy should be carried out is sometimes a ticklish one. I think that a check of the mortality and survival statistics will reveal that many centers in the country are now saving over 50 per cent of these infants. It behooves all of us to be sure that we can offer at our own institution, or at those centers where we refer such infants, a chance for survival in keeping with the level of the better statistics. There are many large hospitals in the country which have not as yet achieved any survivals. Yet there are several with over 100 living patients, some 18 and 19 years of age. In any case, a decision following diagnosis should be made quickly. We don't run into it here. But when I was in Boston, we often had phone calls from some 400 miles up in Maine, asking permission to bring a baby down. The diagnosis had often already been made, but further instructions were needed. Through learning the hard way, I gradually devised a few practical procedures that might also apply to shorter trips.

They are: If possible, send a nurse with the baby, accompanied by the father (if for no other reason than to give consent for operation). An ambulance is not necessary, particularly if there is a portable incubator or carrier for the infant. In Maine there were few of those; automobiles served well. We asked the nurse and the family to wear masks when they were with the baby. Oxygen was usually provided by

cone and small tank. A catheter was usually taped in at a measured point, just short of the point of obstruction, and a syringe was given to the nurse for intermittent aspiration at 15-minute intervals. I usually asked the doctor to give the baby antibiotics but no fluids before starting, and I requested that the nurse keep the infant propped up 20-30 degrees. Perhaps some of these items are debatable, but at least the nurse and the father were kept busy. Preoperative preparation is important, and it certainly should be expeditious. It is rare that a delay of more than 8 to 12 hours can be of benefit to the baby if he is so sick that he needs further care. In most cases the benefit of a longer period of preparation is very small.

I shall not discuss operative procedure except to say that, in general, I think all surgeons agree that division of the fistula and primary anastomosis are of prime importance. The approach is either transpleural or extrapleural. Some omit gastrostomy, some do it routinely, some do it only on indication.

The problem case in the good baby, without other major anomalies, is the case of esophageal atresia without a fistula. In such a situation, the distal esophageal segment is almost invariably quite small and the gap is too long to permit a safe primary anastomosis. Personally, I have come to favor deferring definitive surgery in such infants with the hope of achieving survival; doing a gastrostomy and a cervical esophagostomy under local anesthesia, and then, at age one and one-half or two years, doing a colon transplant retrosternally.

I should like to list the factors that seem important in helping us predict end results in survival. One is the size of the baby. Survival is rare when the weight is less than four pounds. I found one in the records that weighed only 2 pounds, 15 ounces.

The element of prematurity or immaturity is an intangible factor, but certainly the presence of associated major anomalies is particularly important. Many infants that survived had, in addition, an imperforate anus, duodenal atresia, or other obstruction of the intestinal tract that would have been fatal without definitive therapy.

The possibility that open heart surgery will reduce the number of deaths from associated cardiac anomalies is a real one when this age group is eventually invaded. The local anatomical factors are important to us as surgeons – the length of the gap between the ends, the size and location of the fistula, the possible anomalies of the trachea. The

amount of pneumonia is certainly important, and it seems to be moderately well correlated with the age of the baby.

I recall an instance of surgery performed on one survivor at 28 days of age, who was maintained on clyses and suction of the proximal pouch. Early diagnosis, prompt and proper referral, good supportive care, and diligent residents who like to make rounds at two and three a.m. almost with laryngoscope in pocket: these are all essential. Some of the late complications can be fatal but, if anticipated, need not be. Stricture, aspiration, and cough are examples of such.

To conclude, I shall just list some of the other anomalies and briefly outline what therapy has to offer. The whole question of strictures of the esophagus is less important to us because its incidence is not great, but congenital stenosis occurs fairly frequently. As though in preparation for this talk, there was a case in Kings County Hospital last month, with a presenting complaint of anemia. The infant had had nothing but milk for the first 18 months of life and his anemia was the only thing that brought him to the hospital. This condition is often picked up in the first few weeks of life, more often when solid food is first added to the diet. I would say that about half of the stenoses are found in the middle third of the esophagus, lower down than the atretic lesions. Surgical treatment by excision and anastomosis is occasionally required, but dilation is usually satisfactory, and is safer, even if repeated.

Postoperative strictures in the survivors of atresia operations are showing up in large numbers, and these strictures probably provide our largest group of stenotic lesions. I won't discuss those at all.

(Slide) This is just an AP view of an infant with esophageal atresia with fistula, the usual type of lesion. The presence of gas in the abdomen immediately indicates that there is a fistula in conjunction with the pouch with its small amount of the Lipiodol present.

(Slide) This is a lateral view of another infant with marked abdominal distention. Actually, the fistula can be demonstrated here by the air pattern. Occasionally the distention can be a factor so markedly contributing to the respiratory distress that the possibility of help from a preliminary gastrostomy should not be forgotten, particularly if there seems to be diffuse atelectasis, as occasionally seen slowly resolving in the newborn infant.

(Slide) A barium swallow in a three-year-old child: It shows a congenital stenosis, in the middle third, a localized lesion. The final

diagnosis is not easily made with the barium swallow alone but, with the history, the location in the middle third, and no previous surgery, it is almost certain to be congenital in origin. Esophagoscopy shows no evidence of inflammation in such a lesion.

(Slide) Peptic esophagitis has come to the fore in the last few years, particularly in adult patients, since resection of the upper stomach and lower esophagus has become much more common. There have been anastomotic difficulties with esophagitis. The commonly repaired hiatus hernias have also caused revival of interest. In the last few years, cases of peptic esophagitis in infants have been reported in increasing numbers. The mechanisms all have to do with gastro-esophageal incompetence.

It is worth while to consider cases of incompetence as being in one of three groups. The first has been called *chalasia*. In some infants who vomit, usually during the first week, rarely after ten days, the vomitus is more a regurgitation and practically never contains blood or bile. There is not much weight loss but there may be failure to gain. When other causes are ruled out and a barium swallow is done, such infants show free reflux, even with respiration. If the infant is placed in a sitting position and then rocked on its back the esophagus will fill with the thin barium mixture from the stomach. These infants seem to have a patulous gastro-esophageal opening. The esophagus is abnormal, in general quite lax. The exact etiology is not known. Fortunately, this responds to simple supportive therapy, consisting primarily of propping the infant up with a sling or special chair after feedings. In other words, let postural or gravity effects keep down the esophageal reflux, and occasionally thicken feedings to assist this course. Those babies don't often get to the surgeons. They are more likely to be a differential diagnostic problem for the pediatrician.

The remaining two types are associated with a hiatal hernia or true sliding hernia, or possibly with aberrant gastric mucosa, either in island form or in the mucosal junction, resting above the diaphragm, with loss of the normal mechanism for competence. Fortunately, most cases of peptic esophagitis do not require surgery if treated with full recognition of the value of strictly upright posture or, shall we say, steep posture, after feedings and with antacids.

Other lesions which are rare should be reckoned with in our differential diagnosis. Among them is the occasional vascular ring. The usual major symptoms caused by vascular ring are respiratory. Occa-

sionally we have a duplication of the esophagus which gives symptoms by external pressure or by bleeding, and those low in the esophagus are particularly difficult to detect by x-ray or other methods. Skilled fluoroscopy may be necessary.

MODERATOR HUMPHREYS: For a long time Dr. Santulli has been interested in the various problems related to pyloric stenosis or those which have to be differentiated from pyloric stenosis, many of which Dr. Hodes has already mentioned.

DR. THOMAS V. SANTULLI: Most of what I have to say regarding intestinal obstruction in the newborn period has to do with early diagnosis. Although a good many deaths are due to prematurity and to other associated serious anomalies, in many cases the prognosis is directly related to the promptness of diagnosis so that it is imperative to be alert to the possibility of intestinal obstruction in a newborn infant. Actually, groundwork for such a diagnosis can begin even before the baby is born, when one is presented with a family history of intestinal obstruction or of fibrocystic disease of the pancreas in a sibling. Such a history is significant and should make one alert to the possibility of meconium ileus in the newborn baby.

The second condition of importance, which has become quite obvious in the last few years, is a history of hydramnios in the mother. Dr. Richardson has mentioned the association of hydramnios in an otherwise normal mother and upper intestinal obstruction in her infant. In fully 70 per cent of the infants who have an obstruction of the upper intestinal tract, there is a history of hydramnios in the mother. Below the level of 20 cm. beyond the ligament of Treitz, a history of hydramnios in the mother is very rare. Hydramnios should at least make one aware of the possibility of high intestinal obstruction in this unborn baby.

I do favor the passage of a small polyethylene nasogastric catheter as a routine procedure in all newborn babies. It has been so used in Sloane Hospital for the past several years, and so far we have been fortunate in diagnosing intestinal obstruction, suggested very early in those babies who have over 25 ml. of amniotic fluid aspirated from the stomach, especially if it is bile-stained. I appreciate the implications of this, but I am also aware of the early diagnoses that have been made.

In the newborn infant, of course, the earliest sign of obstruction is vomiting and, as Dr. Hodes has indicated, this is a certain type of vomiting. Certainly the baby who continues to vomit, or the baby who

vomits bile-stained fluids, should be considered to have intestinal obstruction until proven otherwise. With a history of vomiting, or with distention or with failure to pass meconium within the first 24 hours, the physician must conclude that this is intestinal obstruction until he knows that it is not. The most important single aid in diagnosis is the plain x-ray of the abdomen. The diagnosis can almost always be made with the plain films of the abdomen, without using a contrast agent.

(Slide) This shows a typical, complete duodenal obstruction – the conventional three-position films. This is a case of duodenal atresia, with no need for contrast media. The diagnosis is easily made.

(Slide) Lower down the intestinal tract, in the jejunum, the problem is still quite simple. The three-position films will make the diagnosis without resorting to any contrast media by mouth.

Up to this point it is simple. Lower in the intestinal tract, in the ileum, or in the colon, the x-rays offer some problems. As you know, in all age groups, it is sometimes impossible to differentiate small from large bowel. In the newborn period this is almost invariably so, and none of the roentgenologists would ever state categorically whether the dilated loop in this x-ray is small or large intestine. This was, in fact, obstruction of the terminal ileum, due to meconium ileus, but on the evidence of the x-ray alone you would be put to it to say whether this is a dilated loop of ileum or colon. Therefore, in these lower obstructions it becomes important at times to differentiate large from small intestine by resorting to a barium enema. As long as the colon can be demonstrated one can distinguish large from small intestine, which is important in enabling one to decide on the proper procedure to follow.

(Slide) Let us consider the problem of the differential diagnosis in the newborn period of distal ileal obstruction and colonic obstruction. The newborn megacolon often presents with signs of low small intestinal obstruction, that is, obstruction in the lower ileum. It is not uncommon to operate on a baby who does have congenital megacolon, in the belief that you are operating for obstruction of the ileum. Here, in the first x-ray, you see a representative picture of a dilated loop of intestine, which could be transverse colon or a loop of ileum. With the barium enema, it becomes obvious that this is transverse colon and therefore the diagnosis of congenital megacolon can be made, even, as in this case, at the age of three days.

(Slide) The congenital atresias of the small intestine are often dif-

ficult to treat, because of the marked disparity in size of the proximal and distal intestine, as shown on this specimen of ileum. The atresias of the gastrointestinal tract are most commonly found in the rectum; then, in order of frequency, in the esophagus, duodenum, ileum, and jejunum. Atresia of the large bowel is extremely rare (exclusive of the rectum).

(Slide) You are all aware that meconium ileus is always associated with fibrocystic disease of the pancreas, and that this is perhaps the most difficult and discouraging form of obstruction to treat in the newborn period. Characteristically, the terminal ileum is obstructed by inspissated concretions of meconium. The colon is very small. It has often been referred to as micro-colon.

(Slide) This slide shows the type of material in the terminal ileum, and it shows this large hypertrophied loop of mid-ileum, which is also characteristic of the disease, containing the viscid and very tenacious tarry-like meconium.

(Slide) This loop of mid-ileum undergoes volvulus even before the baby is born, so that in about 50 per cent of the cases a volvulus, often with gangrene, may occur. Again notice, on the slide, the tiny colon.

(Slide) Malrotation obstructions: I shall not spend any time on these, except to emphasize the ever-present danger of gangrene of the entire midgut if the volvulus becomes tight enough to obstruct the superior mesenteric artery. We have seen it as early as 16 hours after birth. You cannot predict when this will occur. The diagnosis should be made early, and all babies who have malrotation with small bowel obstruction should be operated upon, even though the obstruction may be spontaneously relieved, because if obstruction of the artery does occur, then gangrene of the entire midgut segment results. We have had too many such cases to feel otherwise.

(Slide) Just a few words on hypertrophic pyloric stenosis. This takes us a little beyond the newborn period. As you know, these babies usually begin to vomit in the second or third week of life. Their vomiting becomes more forceful and projectile. They lose weight. They show dehydration and constipation. On examination of the abdomen, large gastric peristaltic waves are seen and the diagnosis is made on palpation of the pyloric hypertrophy in the right upper quadrant. Occasionally it is necessary to resort to a gastrointestinal x-ray series to make the diagnosis. In the oblique views, the long, narrow pyloric canal will be seen, which confirms the diagnosis. X-rays are rarely needed, but there

are times when they must be resorted to following a lapse of days, during which time it was not possible to palpate the mass. We feel strongly that the treatment of choice is surgical. With proper preparation (none of them should be operated upon as emergencies), pyloromyotomy effectively relieves the obstruction and gives gratifying long-term results.

MODERATOR HUMPHREYS: *Dr. Hiatt will discuss lesions of the colon, rectum, and anus. Although Dr. Santulli touched on differential diagnosis to a certain extent, the actual problem of dealing with them is somewhat more complex, and I shall ask Dr. Hiatt to discuss that.*

DR. ROBERT B. HIATT: During the last ten years, there have been advances on almost all fronts in pediatric surgery; but one of the greatest gains has been in the treatment of surgical conditions of the large intestine, rectum, and anus in the newborn and early childhood period, particularly in the management of congenital megacolon and imperforate anus. I shall confine most of my remarks to these two conditions, since they represent more than 25 per cent of all admissions to the pediatric surgical service, of babies with intestinal problems in the newborn period.

I am sure you are all familiar with the progress made in our understanding of megacolon. For a brief review I would have to look at this schematic drawing.

(Slide) In congenital megacolon there is a marked hypertrophy, dilatation in one area, with a much narrower collapsed segment in another area. The aganglionosis begins before the narrow area is reached; roughly it stops at this point, so that this portion, which is the really important portion physiologically, we call the transitional segment. There is so much misconception concerning the pathological physiology of this disease that I should like to show you what happens if you simply resect this transitional segment, which would be similar to what we would call an anterior resection of the rectum, not doing a pull-through procedure.

(Slide) If the transitional segment is resected and anastomosis is done, these patients will do very well for a period of from one year to as long as ten years. I have just recently re-operated on a child that I did over ten years ago, and this is what has happened in all of these patients who have been operated upon in this way — a new transitional segment is formed in the proximal portion of the remaining aganglionic

segment. It is this hypertrophy in the proximal portion of the aganglionic segment that is responsible for most of the obstruction. This segment becomes spastic as a result of feces being pushed into the upper portion of the aganglionic gut. All that anterior resection accomplishes is to convert a standard type of congenital megacolon into a megarectum type.

(Slide) This is what happens in the routine pull-through procedure. An attempt is made to remove not only the transitional segment but the entire rectal segment down to within the anal canal. Consequently, a year or more after the operation, the rectum and colon have returned to normal.

The classical picture of congenital megacolon, in a child who has a protuberant abdomen and is severely constipated, no longer presents either a diagnostic or a therapeutic problem. But it is also true that such classical cases are now practically non-existent; they have all been treated at a much earlier age. Instead, we are now dealing more often with congenital megacolon that produces obstructive symptoms in the newborn period, or congenital megacolon of the megarectum type in which the transitional segment lies just above the anus.

In congenital megacolon which produces symptoms in the newborn, we are faced, as Dr. Santulli points out, with a difficult diagnostic problem, all too frequently mishandled. The reason for error in this age group, as he pointed out, is that the obstructive symptoms are those of small-gut obstruction; and he also cited the assistance a gently administered barium enema could give in making a correct diagnosis. Let me emphasize the word "gentle". We have four children in our series whose rectums were perforated by somewhat over-zealous manipulation. These rectums are very thin-walled and easy to perforate.

In older children, we frequently encounter cases which present the classical picture of megacolon, with constipation, with or without fecal soiling, and in which the barium enema is atypical. The constipation could be either psychogenic in origin or due to congenital megacolon or megarectum. The difference between the two conditions can be distinguished only by means of special diagnostic aids. A presacral airogram in conjunction with the small barium enemas is one helpful procedure. This indicates to some degree the thickness of the rectal wall. If the rectal wall is of normal thickness, it can reasonably be assumed that a psychogenic factor is involved. If there is marked hypertrophy of the rectal

wall, although the lumen may be of normal size, one is probably dealing with megarectum-megacolon. Should the airogram give equivocal results, a biopsy of the rectal wall through the posterior proctotomy approach is indicated. It is important to make an accurate diagnosis in a child who is constipated or incontinent without obvious cause. Anal dysfunction in our culture is the source of great concern, and it is impossible for the family doctor, the internist, or the pediatrician to cope intelligently with this problem unless he first determines whether the difficulty is of psychogenic or structural origin. It is never wise to assume that an infant or young child who has constipation, with or without incontinence, has psychic problems, without first ruling out congenital megacolon associated with a short aganglionic segment.

Now a word about the pre- and postoperative management of megacolon patients: Those of us who have had considerable experience with the care of these patients have come to realize, during the last five years, that the evil spectre of enterocolitis threatens all patients who have congenital megacolon. Megacolon patients are peculiarly susceptible to this strange condition, in both the pre- and postoperative periods. It is characterized by abdominal distention, fever, toxemia, and diarrhea. If not recognized early, it can rapidly progress to the pseudo-membranous type of colitis, and death. It is apparent in our series of over 150 patients, that about 25 per cent have had enterocolitis in some form or another, fortunately usually in mild form. The Micrococcus pyogenes var. aureus (Staphylococcus aureus) can occasionally be found in stool cultures, but in the majority of cases no specific pathogen can be found. Therefore antibiotic treatment of this particular condition has been of limited value. The one underlying factor that seems to control the severity of the symptoms in this type of enterocolitis is intracolonic pressure. If the intracolonic pressure is kept low, the disease is mild and runs a natural course, subsiding in a few days. This low intracolonic pressure usually can be accomplished by frequent rectal treatment in the form of enemata or rectal tube enemata. However, in four children this treatment was ineffectual and temporary colostomy became necessary. One child, who had already reached the pseudo-membranous stage, was immediately improved by transverse colostomy. The colostomy was closed eight months later and the patient has now been well for four years. This child did not develop enterocolitis until three years after the pull-through procedure, and during those three years he was free of

symptoms.

Because of enterocolitis, we no longer try to carry newborn children, who have obstructive symptoms from congenital megacolon, through to the optimum age for pull-through procedure. Instead, as soon as the condition is recognized, we perform a colostomy and then do a definitive pull-through operation at between 12 and 14 months of age. Occasionally, a child's compensatory mechanisms, that is the hypertrophy, are so well established at birth that we carry him to the operative age without colostomy. However, we watch such patients very carefully, instructing the mother to take daily temperatures. Any undue distention and slight fever are usually indicative of impending enterocolitis.

Now a few words about the diagnosis and treatment of imperforate anus: The diagnosis is obvious in most cases, by simply inspecting the perineum of the newborn child. However, two types, fortunately quite rare, might escape notice. The first is the imperforate anus with recto-perineal fistula, which at first glance may appear to be a normal anus. I have seen two adult patients who actually have had recto-perineal fistulas that were not diagnosed.

The second is the so-called type IV imperforate anus in which the anus, although normal, ends in a blind pouch just proximal to it. Therefore it is wise to make a habit of inserting a thermometer, usually the nearest handy instrument for this purpose, into the anus when inspecting a baby's perineum. In recto-perineal fistulas, the anal canal is often angled posteriorly before it enters the true rectum. In the type IV imperforate anus patient it comes to an abrupt stop just inside the anus. The management of imperforate anus with its assorted fistulae has been greatly simplified and improved in the past eight years.

The primary aim of surgical treatment and management is a complete reconstruction as soon as the diagnosis is made. Rhodes, of Philadelphia, did a combined abdominal perineal pull-through procedure for imperforate anus in 1944, but did not publish a report until 1948. By this time, experience with rectal mobilization in congenital megacolon made a more aggressive approach to imperforate anus logical and became universally adopted for all types of imperforate anus in which the rectal pouch is more than 1.5 cm. from the anal dimple. When less than 1.5 cm. from the anus, a perineal approach is usually all that is necessary. However, a word of caution about the imperforate anus patient in whom it appears that only a thin layer of skin exists between

the blind pouch of the rectum and the exterior surface. If possible, resist the temptation to make a simple incision to relieve the obstruction, because this almost invariably results in cicatricial anal stenosis. Because of intrarectal pressure, the perineum is thinned out, giving a false impression of thinness. Actually, it may be a centimeter thick in the relaxed stage. Therefore it is better to do precise anoplasty, mobilizing the distal rectum enough to approximate the rectal wall to the anal skin without tension.

A final word about intussusception, which is today largely treated by barium enema. However, a constant percentage of these patients subsequently does require surgery, either because of perforation or because the leading point of the intussusception may be a polyp, a Meckel's diverticulum, or something of that nature. Therefore it is wise, when treating a child with intussusception by means of intracolonic pressure in the form of barium enema, to have the surgeon informed of the procedures employed so that responsibility can be shared.

MODERATOR HUMPHREYS: *Are there any questions from the floor, in the few minutes remaining?*

DOCTOR: I would like to ask Dr. Hiatt how to distinguish between Type I imperforate anus in which there is an anal stenosis and the Hirschsprung's megarectum.

DR. HIATT: That is a very good question. To do this requires some experience. However, if a tight ring is felt at the anus, this is not congenital megacolon, unless there happens to be associated congenital megacolon with the Type I imperforate anus, of which there is more than average association, in congenital-megacolon patients in this newborn period. When examined rectally, they usually give a characteristic feel of a small dilatable rectum, which, when the little finger is inserted up to the tip, will generally enter the dilated segment, but not always. When the examining finger is removed, a sudden gush of meconium follows, which will temporarily relieve the obstruction. Insertion of the little finger as far as possible in the rectum will, to my mind, provide almost certain diagnosis.

DOCTOR: I would like to ask Dr. Santulli to highlight the diagnostic points of malrotation.

DR. SANTULLI: Most of the time the baby with malrotation will vomit bile-stained and often, brilliant-green fluid. The vomiting may be intermittent because the volvulus may be complete, with obstruction

of the duodeno-jejunal junction, but then relieves itself. The baby who vomits bile-stained fluid like that, who is not distended and who on plain x-ray of the abdomen shows a dilated stomach and duodenum with very little air in the small intestine below, probably has malrotation with a midgut volvulus. Carried one step further, a barium enema will show the colon to be entirely on the left side of the abdomen. We have seen newborn babies with massive gastrointestinal hemorrhage, sometimes associated with vomiting, other times not. These babies may have malrotation with gangrene or with impending gangrene of the midgut. Blood by rectum may be the first symptom, and rather than make a diagnosis of hypoprothrombinemia one should be sure that there it is not malrotation with volvulus.

MODERATOR HUMPHREYS: I think it is fair to say – is it not, Dr. Santulli, that malrotation *per se* causes no symptom. We find some people in adult life with malrotation.

DR. SANTULLI: Yes.

MODERATOR HUMPHREYS: The symptoms associated with malrotation are secondary, due either to adhesions or bands across the duodenum or to volvulus.

DR. SANTULLI: I was assuming that we were speaking of intestinal obstruction on the basis of malrotation. Malrotation need not be associated with symptoms.

DOCTOR: I would like to ask three short questions: The first one, addressed to Dr. Hodes, concerns the number of cases with Hirschsprung's disease with water intoxication from the overuse of water. I think that should be brought out.

DR. HODES: I think Dr. Hiatt can answer. I am not sure that is the correct explanation, because we have seen collapse occur when the enema given was not water but a small amount of olive oil. I think there may be more to this than simply water intoxication. In some cases the collapse may be due to water intoxication, in others there may be other factors. Would you like to discuss this, Dr. Hiatt?

DR. HIATT: I am interested in that comment because we are relatively convinced that it is water intoxication. We once mustered up courage to instill water into a child and followed serially the serum chloride, serum sodium, and determined the plasma volume before and after the enema. The sodium and chloride fell precipitously, while the plasma volume rose, perhaps an indication of certain reflex factors which

are unknown to us. There are, however, patients who will die from being given too much water by enema—this is particularly true in the patient with megacolon.

DR. HODES: I don't want to seem to disagree. In one instance in which the enema was given, I was standing right in the room, and I know that not more than a pint of olive oil was given. That child collapsed and died. No water was given at all. I don't know what the cause of this unfortunate incident was.

DR. HAITT: I have seen patients die in such circumstances. That is what drew our attention to it. We were planning to operate on the patient, and an overzealous resident came by in the middle of the night, thought the patient was too distended for operation, started giving enemas, with the result that shock, convulsions, and death ensued.

DOCTOR: Does that occur with chronically repeated enemas by the mother?

DR. HIATT: I recognize that 10-15 per cent of all my patients have had water intoxication.

SAME DOCTOR: One other question: What is, approximately, the length of time that it takes for dilated aganglionic segments to contract after the pull-through type of operation?

DR. HIATT: Approximately a year, maybe less.

DOCTOR: What are the percentages of patients on whom you have operated, who have grown either to adolescence or adult life with the classical Hirschsprung's disease? It does occur, I know, in adults.

DR. HIATT: How many children have grown to be adults with congenital megacolon?

DOCTOR: How many adults did you have to treat?

DR. HIATT: Eight to ten adults, as a rough guess.

DOCTOR: That about agrees with Swenson's series, as he reported a few weeks ago in Boston.

MODERATOR HUMPHREYS: *Is it your impression, Dr. Hiatt, that individuals who reach adult life with megacolon probably have a less severe type of megacolon than those who show it in infancy, or do you think that most of the infants would get over the acute symptoms and go on with their intermittent or chronic symptoms into adult life?*

DR. HIATT: I think I would rather give certain mothers the credit for raising children to adulthood. I have often thought of forming a club of megacolon mothers, because they have all been through five to

ten years of severe stress, during which they rely upon their innate intelligence in keeping the child alive. In most cases, those who have survived to adulthood have had very intelligent mothers who worked assiduously with them, sometimes even ignoring professional advice to achieve this goal. Actually, you can have a very severe type of congenital megacolon. It depends upon your criteria for severity, and the length of the segment is not the criterion for severity. It is the peculiar nature of the compensatory mechanisms for overcoming the obstruction. Certain children will always be a little in advance with their compensatory mechanisms, hypertrophy and dilatation. If they stay ahead, they are not obstructed but the disease is progressive. It never remains static. It grows progressively worse, year after year. I am sure there are not many magacolon patients who have survived past 30 years of age.

DR. SANTULLI: May I ask a question?

MODERATOR HUMPHREYS: Certainly!

DR. SANTULLI: Would you not say that the baby with the longer aganglionic segment is apt to have the more severe disease?

DR. HIATT: Those who have the longer aganglionic segment are those who require immediate colostomy in the newborn period. There are a great number of patients who have a long segment, to the splenic or hepatic flexure. Some of these will do well for quite a period of time without operation. We find, occasionally, a patient who is not operated on until five or six years of age, who has a higher transitional segment. In general, there is some slight factor in which the length is involved. It is that transitional segment which is the crux of the situation in maintaining the delicate balance between obstruction and mechanisms for overcoming obstruction.

MODERATOR HUMPHREYS: *Are there other questions?*

DR. HODES: I shall address one to Dr. Hiatt: The question concerns the membranous colitis about which you have spoken. Pathogenic organisms are not, in general, found. I take it from what was said before that you do not regard this as simply an infection of the colon. Is that right, so far?

DR. HIATT: I, frankly, do not understand this peculiar condition. I am not sure whether these patients with enterocolitis have the same type as those we see in adults following surgical procedures, who develop the so-called staphylococcal enteritides. As far as I know, there is no absolute proof that in the adult the staphylococcus is the pathogenic

agent. In children who don't respond to conservative treatment of enemata and rectal tube to keep the abdomen deflated, the only procedure that we have to fall back on is the colostomy. It is really startling to see a very toxic, anorexic, very sick, almost moribund child converted within a few hours into a child who wants to get up and who practically runs around the ward a few hours after a colostomy. Observation of two or three of these experiences has led me to believe that it is not just infection. It is what I call colonic decompensation. Something has happened, often in the form of an intercurrent respiratory disease, viral infestation you might say, which makes the colon lose its efficiency. It will begin to dilate and not be able to contract. Then a toxic state results which might well be due not to infection but just to the normal inhabitants of the colon.

DR. HODES: I was thinking more of the inflammatory part of this phenomenon. I have seen three children in the course of infection with Salmonella, doing very well, who have suddenly shown intestinal symptoms. One of them was operated on and had, not in the colon but in the small intestine, the findings which you have described. One of them died. The explanation that I offer is that this reaction is due to local Shwartzman phenomenon. It occurs to me now that this might be happening with organisms which we don't ordinarily consider to be pathogenic. I wonder whether the E. coli that you found in these cultures were examined to determine whether they might be enteropathogenic.

DR. HIATT: You might be on the right track.

DR. HODES: I volunteer to type them for you.

DR. HIATT: Fine, delighted!

MODERATOR HUMPHREYS: *Are there any other questions?*

I should bring out that we have necessarily concentrated on congenital lesions of one sort or another, if one grants that a lesion such as pyloric stenosis is actually congenital. There are, of course, quite a number of ordinary causes of vomiting which require surgery, such as appendicitis, which do also occur in childhood. We have assumed that you knew about these. The conditions which concern us most in dealing with the infant are congenital anomalies, of which the common ones have been mentioned. There are, in addition, rarer ones. These we did not have time to discuss.

SINGLE EPISODE OF CONFUSION WITH AMNESIA*

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EPISODES of confusion with memory loss and temporal amnesia are frequent symptoms of brain disease and have a varied etiology. Among the more common causes are head trauma, senile and presenile dementia, diffuse vascular disease of the brain, metabolic disturbances which affect the brain, such as hypoglycemia, intoxications such as acute alcoholism, psychomotor epilepsy and the post-ictal states of seizures caused by brain tumor and other disease[1].The symptom complex about to be described cannot be grouped, however, with any of these entities because the characteristic feature of the syndrome is the singleness of the attack without recurrence over a period of years[2,3].

In general, the typical history of this unique syndrome is that of a patient past the menopausal age, who suddenly becomes disoriented and shows a severe loss of memory. The subject becomes repetitious and incessantly asks the same question throughout the period of mental confusion; the thought content and conversation appear to revolve about the subject's loss of memory. Such patients may know their name and recognize their nearest relatives but most facts which are related to their daily activities are forgotten. Examination of these patients during the period of mental confusion reveals no significant evidence of sensory or motor aphasia. The slight defects which appear on routine examinations for aphasia are of the type to be expected in one who has a severe loss of memory, especially for immediate or recent events; the remote memory is only moderately impaired. The patient may not recall the name of an item or of a stated fact after repeated testing; the inability to name an object may suggest aphasia, but actually the naming defect is minimal compared with the existing severe memory deficit. On specific testing there is often disorientation for dates and for persons who are not relatives or close friends. Although in home surroundings the patient

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rarely shows disorientation for space, when outside or traveling he often gets lost. Simple calculation and even serial subtractions may be well performed and while general information is defective, this seems to be related to poor retention of immediate happenings. Despite the defect in memory, there are no confabulations and there is no denial of illness. The patient usually has some insight into his memory deficiency and all show great concern about their inability to remember; some cry and appear quite agitated throughout this period of confusion. They are very inquisitive about their mental state, asking such questions as: "What is the matter with me?–why can't I remember–I'm worried." The patient appears perplexed and bewildered and constantly repeats the same questions. Not only do they ask the same things over and over, but often go through the same motions of asking. There is marked perseveration in thought, speech and total behavior. The entire episode of mental confusion and repetitiousness may last anywhere from one to six hours until the patient has completely recovered. However, in some cases, the recovery period may be as long as 48 hours. Improvement is gradual over a matter of hours, and following recovery there is a temporal amnesia for all events that transpired during the period of confusion. Ultimately the patient becomes normal in behavior and thinking.

The following case history illustrates this particular syndrome. Detailed observations were made by the patient's daughter, who happened to be a physician.

Case History: The patient, Mr. H., a school teacher, age 55 years, and his wife left home in Brooklyn, New York on November 30, 1957 to meet their married daughter, a physician, Dr. G., in a department store. They met at 12:00 noon and he seemed normal in his conversation and behavior. At 1:30 P.M., he excused himself and he did not return until 2:05 P.M., when he was found standing at a distant counter, apparently confused and bewildered. He asked his daughter where he was. He did not know what he was to do or where he was going. He said that he thought that he had been sick, and he had something wrong with him, maybe "cramps". He appeared quite warm and dazed. He denied having fainted, fallen or striking his head. He did not appear disheveled. There was no obvious weakness, ataxia or dysarthria. He was taken home and, while in a taxicab, he responded to questions in short syllable words and continuously said, "I have no money". While saying this, he pulled out several money bills from his pocket and then replaced them. One or two minutes later, he repeated his statement, "What am I doing here? How did I get here? By cab? Where was I?" His daughter told him he was shopping in a department store. Again he repeated, "What was I doing here?"

The daughter again answered, "You were shopping". The patient asked, "Was I alone? Who was with me?" He was told that his wife and daughter were with him. The patient replied then, "Isn't it amazing? I can't remember!" These questions were continuously repeated almost all afternoon and evening. He also said, "What has happened to me? Did I have a lapse of memory? Is my blood pressure high or low? What is the matter?" When his daughter tested his mental and speech functions, he said that Roosevelt was President before Eisenhower. He gave the correct addresses of two apartments in which he had lived, one in May 1956 and the other in 1937. He did not remember that they had been planning to have company that evening.

Examinations were made during the entire period of confusion by Dr. G. She carefully observed the patient, performed neurologic, mental and aphasic tests and recorded the blood pressure several times. At 3:00 P.M. on November 30, 1957, the blood pressure was 160/90, at 9:00 P.M. it was 134/88 and the pulse was 92. On December 1, 1957, the blood pressure was 178/74. The neurologic status during these periods was essentially negative except for the findings of November 30th. The patient was disoriented and said that it was December 1959. He was uncertain as to the date and he did not know whether it was Saturday or Sunday. Orientation for familiar people and places was good. He knew that he was in his daughter's house but he could not give the address. There was a marked loss of memory for most recent events. He remembered in what school he taught and that "the Monroe Doctrine was signed on December 2, 1923". Because he had had nothing to eat since breakfast, it was felt he might have hypoglycemia. He was given ice cream and other food but there was no change in his mental status. At 6:00 P.M. he had an electroencephalogram performed at The Mount Sinai Hospital; this record showed no abnormalities five hours after the onset of mental confusion. The neurologic examination at this time and subsequent tests revealed no significant defects. There were only occasional errors in naming objects, as reported by the neurology house staff at The Mount Sinai Hospital; a ball point pen was called a fountain pen. When asked what kind, he said, "You know—one of those fancy gadgets you write with." When shown shoelaces he said, "You tie your shoes with them." When shown the cuff on trousers he said, "You know, the bottom of trousers." He had no difficulty in naming other test objects or in the remaining tests for aphasia. He could repeat Methodist Episcopal Church several times but could not remember it ten minutes later. He could spell the word "world" backwards and forward. He was able to read a complex passage and relate the meaning but immediately thereafter was unable to remember the content. Calculation was seemingly excellent. When given a complex passage to write from dictation, he did well. Two to three minutes later, however, he could not remember that he wrote it. On returning home, after the electroencephalogram, he asked whether he had been sleeping and he complained that he was unable to remember anything that had happened during the day. At about 8:00 P.M. he remembered his current address and at 10:00 P.M.

he recalled most other events which had transpired during the forenoon. However, he was still not mentally clear when he went to sleep. On the following day he remembered almost all occurrences of the previous day until about 1:30 P.M., when the mental confusion had its onset. There was virtually complete amnesia for all events from 1:30 P.M. until the early evening hours of November 30, 1957. He continued to complain of "grogginess". About 48 hours after the onset of his illness, he felt better and returned to work as a school teacher.

Reexamination of this patient in July 1959 disclosed no abnormalities of the nervous system and there had been no recurrence of the episode of confusion.

Although this patient was not seen personally by the author during the first few hours of mental confusion, some of the other patients in this series were studied during the acute episode. All patients showed severe loss of memory, marked perseveration, but no aphasia. The most remarkable feature about this clinical entity is that there have been no recurrences. All of these 26 patients have been reevaluated and none has had a return of this syndrome. In some, there was no recurrence even after an interval of nine years. It is this lack of recurrence which makes the syndrome unique and difficult to interpret. None of these patients had a history to suggest such clear-cut etiologic entities as brain tumor, head injury, toxic-metabolic disorders, acute cerebrovascular accident or convulsive disorder. Clinical examinations during and after the acute episode did not reveal significant changes which would establish a clear diagnosis.

Various laboratory tests, including blood chemistries, spinal fluid examinations, electroencephalograms, skull x-rays and pneumoencephalogram failed to disclose manifest disease of the brain. Although electroencephalograms were performed in most of these patients, only a few were taken during the episode of confusion and these were negative. It is not surprising, therefore, that the records obtained after the attacks were generally normal.

Discussion

This case history is very similar to the others in this series. In considering the location of the disorder, there is no doubt that the mental syndrome observed in these patients was due to brain dysfunction. Although mental confusion is usually the result of diffuse cerebral impairment, there are some who believe that loss of memory may be due to a

localized process. However, the exact site is difficult to pinpoint. Memory deficits have been attributed to lesions of the frontal and, more recently, temporal lobe[4]. Although it has been claimed that loss of memory is due to a lesion in the temporal lobe, it may also occur in lesions of the frontal or other regions of the brain. Actually there is no convincing evidence to indicate that a lesion limited to one specific area of the brain will result in memory loss of the type described in this communication. In general, it would appear that confusional states with difficulty in memory are due to a disturbance in total cerebral function, such as found in the toxic-metabolic states, diffuse disease of the brain, or in postcerebral concussion states. It should be borne in mind that when episodes of confusion occur in patients with localized tumor, scar or other focal brain lesions, the spells may be due to a convulsive discharge and not necessarily be due to alterations of function in one specific region of the brain. Thus, a lesion in the frontal or temporal lobe may give rise to a momentary seizure, followed by a prolonged period of confusion. Subsequently there is amnesia both for the seizure and the period of confusion. It is the convulsive discharge which influences the function of the entire brain. This seizure is often accompanied by diffuse electrical dysrhythmia, as manifested in the electroencephalogram[5]. The confusional state and the temporal amnesia which follow the idiopathic seizure may be considered the behavioral manifestations of diffuse cerebral dysfunction, which may or may not be due to a focal discharge from a scar in one lobe of the brain.

It is well known that an acute lesion in the frontal lobe, such as those induced by lobotomy or lobectomy or one which results from an occlusion of branches of the anterior cerebral artery, may cause a severe memory deficit. With this type of lesion, however, there are many other symptoms, such as confabulation, retardation in thought and motor performance, delayed reaction time, sphincteric dysfunction and denial of illness. It should be emphasized that all of the latter symptoms were conspicuously absent in the 26 patients described in this series.

Studies in the experimental animal (primates) also fail to indicate that a lesion in a specific area of the brain will cause a defect in memory; even special memory functions cannot be localized. There is no localization of special memories in any one portion of the cerebral hemisphere. It would seem that the anatomic substrate for the syndrome herein described is the entire brain and not a focal region. The etiology of the

transient syndrome of memory deficits, confusion and amnesia, without recurrence of the episode, is just as obscure as the anatomy of the lesion.

The following etiologic categories will be discussed:

a) *Vascular disease group:* In considering the etiology of this syndrome, it should be emphasized that most of the patients in the series had a history of serious cardiovascular or renal symptoms prior to the episode. There is no doubt that some of them had arteriosclerotic processes, including myocardial infarction, but none showed conspicuous focal cerebral disease or chronic memory loss. Some had transient changes in blood pressure; in a few, the blood pressure rose, while in others it dropped. A follow-up in some of the other cases revealed that one patient had a coronary occlusion four years after the episode of confusion with amnesia; still another had fundal hemorrhage of unknown origin and later rectal bleeding. These are examples of vascular disturbances but they are of the type which might be expected in the general population in this age group. If this syndrome was due to a specific vascular dysfunction of the brain, one would expect a greater incidence of this disorder in the general population. Moreover, recurrences of such episodes within the same individual would be common. As for an occlusion of a specific cerebral vessel, there is no single artery in the brain which, if occluded, would cause a sudden onset of the syndrome herein described. An occlusion of one anterior cerebral artery or "spasm" of the anterior communicating artery might conceivably produce severe mental confusion with subsequent amnesia. However, in the cases in which amnesia was described after surgical occlusion of one anterior cerebral artery, there were many other symptoms. Marked bradyphrenia, bradykinesis and denial of illness were also conspicuous. As a rule, mental changes caused by vascular disease, except in cases of hemiplegia or aphasia, are due to diffuse cerebral involvement. Diffuse cerebral vascular disease can give rise to periods of confusion. In the chronic cases of arterial disease, recurrences of attacks are frequent, and more often there are persistent mental changes in the background.

b) *The dementias due to "chronic brain disease":* The syndrome of a single, short episode of mental confusion with amnesia cannot be classified as a type of dementia, whatever the basis. In senile and presenile dementia, periods of confusion are common and there may be daily recurrences. Patients with Alzheimer's or Pick's disease may have several episodes a day. As a rule, the episodes appear late in the course of the

disease and furthermore, between attacks, the patient with a dementia is manifestly confused and psychotic. By the time amnesia occurs there is usually a long history of a chronic brain syndrome.

c) *The convulsive group:* The syndrome of isolated amnesia might be mistaken for a postconvulsive confusional state. Periods of confusion with amnesia are not infrequent in seizure disorders[5]. However, in the latter, the duration of the attacks is usually momentary or for a few seconds and recurrences of the episodes are frequent. In so-called "psychomotor epilepsy" or "temporal lobe epilepsy", the confusion may last several minutes to hours. Although this type of seizure may closely resemble the syndrome described, there is usually no complaint of trouble with memory on the part of the patient. Again the most significant differential point is that the "paroxysms" of mental confusion recur at odd and irregular intervals. Moreover, there is often a history of concomitant petit mal or grand mal seizures. In an analysis of the series of 26 cases considered in this communication, none had a history of a seizure or its equivalents. Some of these patients manifested an abrupt alteration of behavior, almost suggestive of a seizure. However, there were no other symptoms, signs or laboratory evidence indicative of a convulsive disorder. Moreover, these patients had no recurrences as would be expected if they indeed had seizure disorders.

d) *Toxic-metabolic group:* In hypoglycemic or uremic states or in acute alcoholism, episodes may occur during which the patient is confused and disoriented, shows defects in memory and subsequently has amnesia for the entire episode. It is well known that a man may take several "drinks" and behave in an apparently normal fashion, except for euphoria and slight memory deficit[6]. He may see members of his family and carry on a conversation and yet forget everything he did by the next morning. Thus, the drinker may not recall what transpired during the period in which he had "one or two cocktails" and even how he got home. He may forget whether he was driven home or what he said during the time he was intoxicated. This type of amnesia is not uncommon. The distinguishing feature in these cases is the history of excessive drinking. This establishes the diagnosis. In hypoglycemia, uremia, hypercholesteremia, hyper- or hypocalcemia, etc., recurrences of mental confusion are common. Laboratory tests often disclose the nature of the metabolic disorder.

e) *Aphasia and focal brain disease:* Another condition which must

be distinguished from this syndrome of memory loss is an episode of aphasia. The patient with acute transient attacks of aphasia may manifest apparent defects in memory and may also sound confused in his speech, be unclear in his thinking and show perseveration. One inexperienced in neurology may confuse this speech disorder with acute mental confusion. Conversely, the attack of mental confusion may be mistaken as an acute aphasia. In this situation, the aid of an experienced neurologist should be sought for the differential diagnosis. In the patient with aphasia, there may be other signs of focal cerebral disease, e.g., right facial weakness or a right homonymous hemianopia in a right-handed individual. Abnormalities of the electroencephalogram are common. On the other hand, in the patient with the acute memory loss and temporal amnesia, there is the incessant questioning as to what happened to him and why the loss of memory. The aphasic elements are minimal and limited to an occasional defect in recalling names of objects. Abnormalities in the electroencephalogram are rare.

f) *Psychogenic group:* The possibility of a psychogenic disorder as the basis for this syndrome should also be considered. In hysterical amnesia the patient is unable to recall any fact, such as names or events which may be associated with his identity, particularly events in connection with a painful situation. In so-called "malingering", the subjects forget what it is to their advantage to forget. Unpleasant experiences are not recalled. At times there is little distinction between intentional forgetting and hysterical amnesia. In either case, the speech is often clear. These patients are usually younger and the available history reveals that there are many emotional problems. Special tests may reveal no loss of memory for immediate events during the period of amnesia. The patient appears calm and does not manifest concern or anxiety about his status. There is no perseveration of speech or thought. Also of significance is the fact that when patients with hysterical or voluntary loss of memory recover, some of them can recall all events which occurred during the "amnesic" period. In other words, there is no true amnesia for the period of hysterical loss of memory. Patients with hysterical amnesia can often be "cured" with the intravenous administration of sodium amytal.

In amnesia associated with schizophrenia, the syndrome may be similar to that found in hysteria. However, there are other symptoms in the illness which will reveal the nature of the disorder, such as bizarre

behavior, dissociation of affect and a history of paranoid, catatonic or hallucinatory experiences.

g) *Trauma:* Head trauma, depending on the severity of the blow, may cause transient mental confusion, impairment of memory and a subsequent temporal amnesia. In fact, the clinical picture may closely resemble the syndrome observed in the 26 patients of the present series. The chief distinguishing features are the ever-present history of head trauma, frequent signs of external head injury, less frequent evidence of skull fracture and changes in the electroencephalogram. Occasionally, because of the amnesia caused by trauma, no history of injury can be obtained, and when the signs of head trauma are absent, it is almost impossible to make the diagnosis. However, in the series herein described, there was no history of head injury. In most instances, the episode occurred suddenly while the patient was either walking, sitting, eating or performing any other act in the routine of daily living.

In summary, none of the various etiologic categories considered explain the syndrome observed in the 26 patients. Perhaps a transient circulatory disturbance of the brain would be the most acceptable. Theoretically, a single episode of interruption of the blood supply by the anterior cerebral artery or its branches or the anterior communicating artery may produce the symptoms described. The vascular theory is considered because of the age group in which the syndrome appeared; moreover, some of the patients in this series showed transient changes in blood pressure, and in a few there was a transient rise in blood pressure during the period of the confusion. However, one must consider that this transient blood pressure rise could have been due to the excitement the patient goes through during this period. Often the patient is anxious and shows great concern about the memory loss. Some patients become agitated and cry throughout the entire period.

The syndrome of mental confusion and temporal amnesia is probably seen in the practice of medicine more often than it has been described. There are very few descriptions of such cases, although recently Doctors Fisher and Adams[3] reported a group at the 1958 meeting of the American Neurological Association. When the general practitioner or internist sees a patient with the syndrome of sudden loss of memory and confusion, the tendency is to classify the condition as a "minor stroke", "cerebral accident" or a "cerebral spasm". This labeling of the syndrome might be acceptable to the patient and family, but it is hardly

a true picture of the pathogenesis. There is no doubt that there is cerebral dysfunction but the exact site and etiology are not known.

Since there have been no autopsies in this series of cases, we must resort to other means of classifying the syndrome. As is obvious from the foregoing discussion, no anatomic or etiology classification of the 26 patients with episodes of defective memory and subsequent amnesia can be made at this time with any degree of certainty until clinico-pathological correlations have been made. Whatever the anatomy or the etiology of the syndrome, it is the abruptness of onset and lack of recurrence of the episode which distinguishes this group from those considered in the differential diagnosis.

Since the episode of memory loss is of such short duration, no treatment has been attempted. The patients improved rapidly, and most significant is that there have been no recurrences. It is important to recognize that there is such a unique syndrome, chiefly because the prognosis is the most benign of all the categories considered.

Summary

A series of 26 patients were observed to have a single episode of confusion which lasted several hours. All of them were past the age of 50 years. The onset of the attack was sudden. The patient has a severe loss of immediate memory, incessantly repeating questions, and not infrequently he shows anxiety about his mental state and his inability to remember. He may be completely disoriented, and may get lost, if he happens to be traveling. The marked mental confusion can last anywhere from one to as long as 48 hours before complete recovery ensues. Following this, there is a complete amnesia for all events that transpired during this period. Of interest and significance is that only one such episode occurred and there have been no recurrences, even in patients who have been observed for periods up to ten years.

The anatomy and pathology of this condition are unknown since there have been no autopsies in this series. The etiology is just as obscure. Hysteria was excluded on clinical grounds. None of these patients whom we studied in detail showed evidence of a neoplasm, trauma, infection or toxic-metabolic disorder. There was no history of alcoholism. Although there was no proof that the syndrome was caused by an occlusion of a single vessel, a general circulatory dysfunction of the brain could produce this type of a clinical picture.

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THURSDAY
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1960

CAUSATION, EPIDEMIOLOGY AND TREATMENT OF COMMON POISONS

Moderator: HAROLD JACOBZINER—*Assistant Commissioner, Department of Health, City of New York; Associate Professor of Clinical Pediatrics; Associate Pediatrician, New York University-Bellevue Medical Center*

Members: MILTON HELPERN—*Chief Medical Examiner, City of New York*

WALTER MODELL—*Associate Professor of Pharmacology, Cornell University Medical College; Associate Visiting Physician, Bellevue Hospital*

BARBARA A. PARKER—*Assistant professor of Medicine, New York University College of Medicine*

MR. HARRY W. RAYBIN—*Technical Director, New York City Poison Control Center*

THURSDAY
April 21
1960

PATHOGENESIS AND MANAGEMENT OF ASCITES

Moderator: FRANKLIN M. HANGER—*Professor of Medicine, College of Physicians and Surgeons, Columbia University; Attending Physician, Presbyterian Hospital*

WILLIAM J. EISENMENGER—*Assistant Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, Lenox Hill Hospital*

JOHN M. LARAGH—*Assistant Professor of Clinical Medicine, College of Physicians & Surgeons, Columbia University; Assistant Physician, The Presbyterian Hospital*

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DOSAGE: For most adult patients the optimal dosage of Aldactone, brand of spironolactone, is 100 mg. four times daily. Aldactone should be administered for at least four or five days before appraising the initial response, since the onset of therapeutic effect is gradual when it is used alone. Aldactone manifests accelerated activity with greater response as early as the first and second days when used in combination with a mercurial or thiazide diuretic.

SUPPLIED: Aldactone is supplied as compression-coated yellow tablets of 100 mg.

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APRIL 28—GLOMERULONEPHRITIS AND PYELONEPHRITIS (panel): Section II—William Goldring, moderator with Herbert Chasis, John P. Merrill, Conrad M. Riley, and George E. Schreiner

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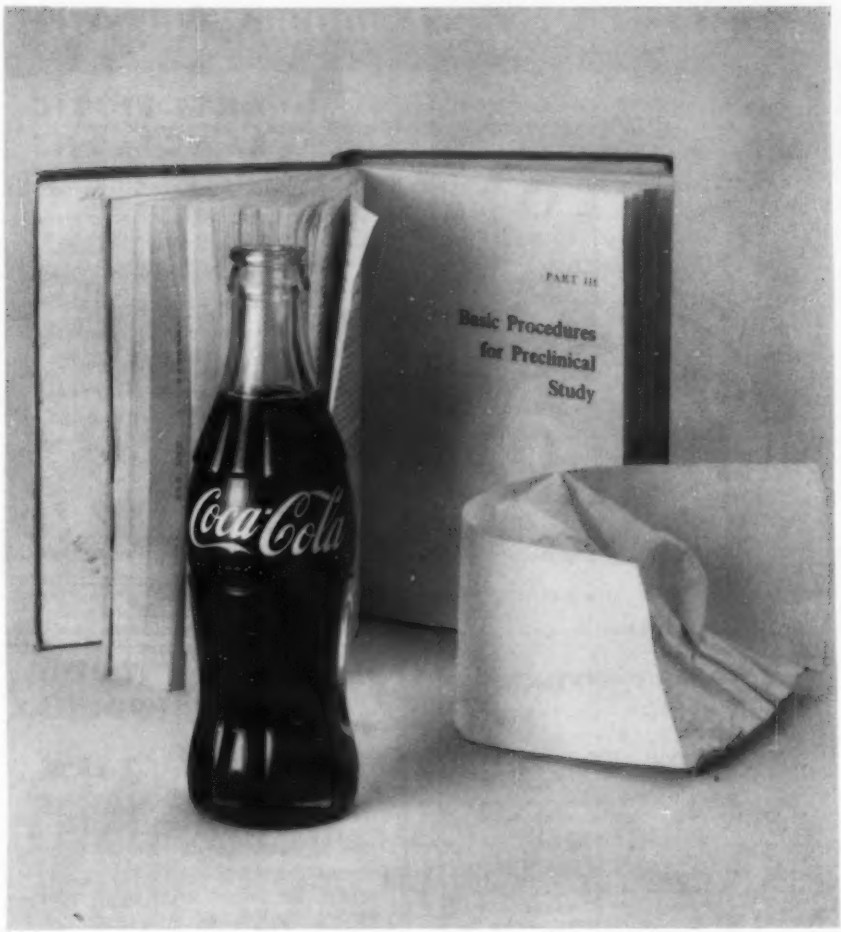

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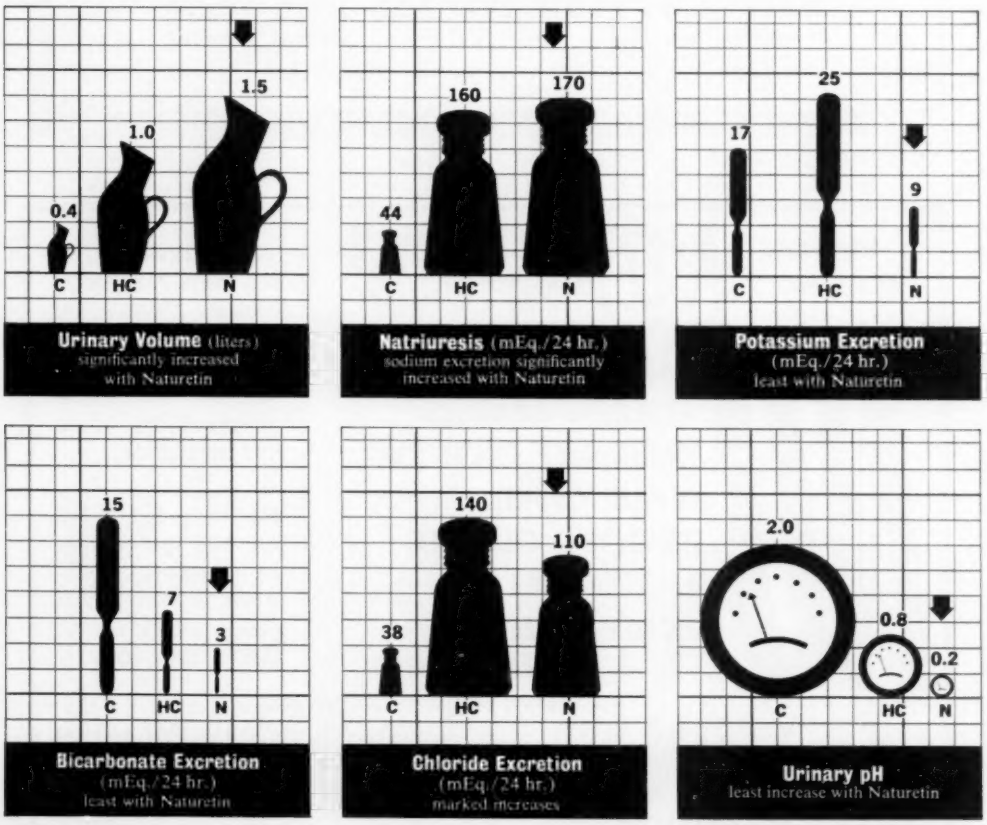
Comparison of electrolyte excretion pattern for the 24 hours following typical doses of chlorothiazide, hydrochlorothiazide, and Naturetin[1]



Typical Doses: Chlorothiazide—1,000 mg.; Hydrochlorothiazide—50 mg.; Naturetin (Benzydroflumethiazide)—5 mg.

1. Adapted from: Ford, R. V., Squibb Clin. Res. Notes 2:1 (Dec.) 1959.

A single 5 mg. tablet once a day provides all these advantages[2]

- prolonged action – in excess of 18 hours
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- greater potency mg. for mg.—more than 100 times as potent as chlorothiazide
- potency maintained with continued administration
- low toxicity – few side effects – low salt diets not necessary
- comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin disclose that smallest doses of Naturetin produce greater weight loss per day
- in hypertension, Naturetin, alone or in combination with other antihypertensives, produces significant decreases in mean blood pressure and other favorable clinical effects
- purpura and agranulocytosis not observed
- allergic reactions rarely observed

[2]Reports (1959) to the Squibb Institute for Medical Research.

Naturētin – *Indications:* in control of edema when diuresis is required, in congestive heart failure, in the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs (certain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb Rauwolfia Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents.

Contraindications: none, except in complete renal shutdown.

Precautions: when Naturetin is added to an antihypertensive regimen including hydralazine, veratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all preparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous drop in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin regimen . . . in hypochloremic alkalosis with or without hypokalemia . . . in cirrhotic patients or those on digitalis therapy when reductions in serum potassium are noted . . . in diabetic patients or those predisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs—leg or abdominal cramps, pruritus, paresthesia, rash—suggestive of hypersensitivity, are noted.

Naturētin – *Dosage: in edema,* average dose, 5 mg., once daily, preferably in the morning; to initiate therapy, up to 20 mg., once daily or in divided doses; for maintenance, 2.5 to 5.0 mg., daily in a single dose. *In hypertension:* suggested initial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending on the individual response of the patient. When Naturetin is added to an antihypertensive regimen with other agents, lower maintenance doses of each drug should be used.

Naturētin – *Supplied:* tablets of 2.5 mg. and 5 mg. (scored).

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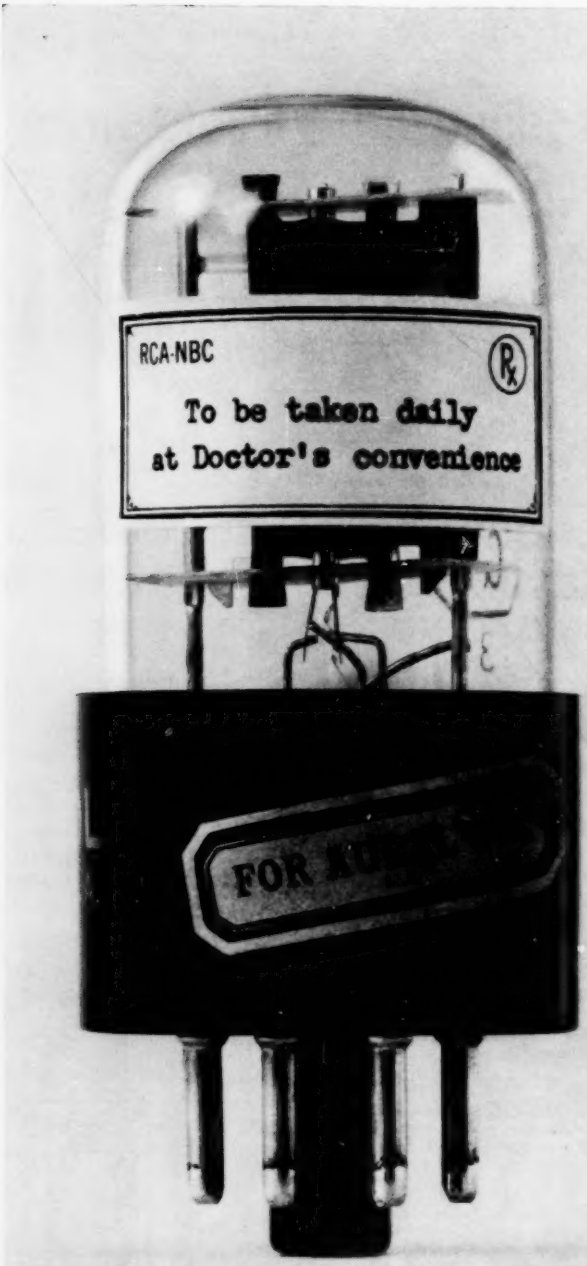

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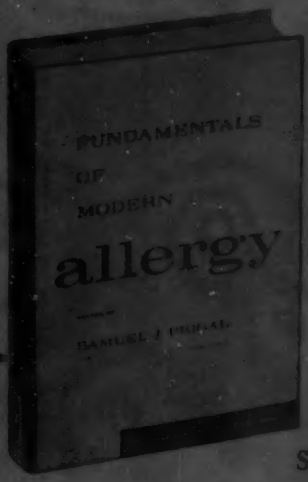

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